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MECHANISM OF EDEMA OF THE RENAL TYPE

STUDY ON BASIS OF CHANGES IN WATER CONTENT OF BLOOD AND IN PROTEIN CONTENT OF BLOOD PLASMA DURING CYCLE OF EDEMA IN CHILDREN

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A knowledge of the changes that occur in the water content of the blood during the development and subsidence of edema of the renal type should help to disclose the mechanism of the production of the edema. For example, if the edema is due to an insufficient elimination of water by the kidneys, and this is believed by von Noorden [1] to be a factor at least in some cases, a high content of water in the blood might be expected during the development of edema. If the edema is due to retention of water by the body tissues, as Fischer [2] believes, the water content should presumably be low during the developmental stage (unless one conceives of a concurrent edema of the blood), and should approach a normal or higher than normal level just preceding and during diuresis and loss of edema. Likewise, if Epstein's [3] theory is correct, that edema in chronic parenchymatous nephritis is the result of a low osmotic pressure of the blood due to a deficient concentration of protein in the plasma, then the water content of the whole blood should be low during the development of edema and higher just preceding and during subsidence of edema. On the basis of his theory, however, a decrease or an increase of the protein content of the plasma should precede a decrease or an increase in the water content of the blood.

Although considerable work on the concentration of the blood and on blood and plasma volumes in edema of the renal type has been reported, the results are in rather poor agreement. There is a sub-

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1. von Noorden, C.: Handbuch der Pathologie des Stoffwechsels, Berlin, A. Hirschwald, 1906, vol. 1, p. 1043.

2. Fischer, M. H.: Oedema, New York, John Wiley & Sons, 1910.

3. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.

stantial accumulation of data showing the presence of a low concentration of protein in the plasma in edema of nephrosis and of glomerular nephritis with nephrotic syndrome, and there is a tendency at present to attribute the production of edema to the deficit of plasma protein in these conditions. A good review of the literature on these subjects may be obtained from the writings of Loeb,[4] Van Slyke and co-workers,[5] Lovett,[6] Leiter [7] and Elwyn.[8]

Evidence tending to indicate a low content of water in the blood in the early phase of renal edema, especially of the nephrotic type of edema, is furnished by Keller,[9] who found abnormally concentrated blood in the early stage of nephrosis at the time of greatest edema. Similarly, Nonnenbruch,[10] while finding polyemia and hydremia in the majority of cases of renal edema, found the concentration of the blood to be normal or even greater than normal in some cases, particularly in the early phase of nephrotic edema. Both of these workers base their conclusions on changes in erythrocyte counts.

On the other hand, on the basis of erythrocyte counts, Frey [11] stated that hydremia is found in nephrosis; and from refractometric measurements of blood serum, Widal [12] thought that polyemia was a condition leading to edema, and Reiss [13] stated that edematous nephritic patients often have hydremia. Veil,[14] though he found normal concentrations of water and sodium chloride in the blood in tubular nephritis, believed that a transient hydremia and hyperchloremia occur and are followed

4. Loeb, Leo: Edema, Medicine **2**:171, 1923.

5. Van Slyke, D. D.; Stillman, E.; Möller, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257, 1930.

6. Lovett, B. R.: The Quantitative Relation of Serum Albumin and Globulin, Arch. Path. **4**:984 (Dec.) 1927.

7. Leiter, L.: Nephrosis, Medicine **10**:135, 1931.

8. Elwyn, Herman: Edema and Its Treatment, New York, The Macmillan Company, 1929.

9. Keller, cited by Volhard, F., and Fahr, T.: Die Bright'sche Nierenkrankheit, Klinik Pathologie und Atlas, Berlin, Julius Springer, 1914, p. 86.

10. Nonnenbruch, W.: Ueber extrarenale Oedemgenese und Vorkommen von konzentriertem Blut bei hydropischen Nierenkranken, Deutsches Arch. f. klin. Med. **136**:170, 1921.

11. Frey, W.: Die hämatogenen Nierenkrankheiten, Ergebn. d. inn. Med. u. Kinderh. **19**:422, 1921.

12. Widal, F.; Benard, R., and Vaucher, E.: L'hydrémie chez les brightiques et les cardiaques oedémateux: son étude à l'aide de la méthode réfractométrique; comparaison de ses variations à celles du poids, Semaine méd. **31**:49, 1911.

13. Reiss, E.: Die refractometrische Blutuntersuchung und ihre Ergebnisse für die Physiologie und Pathologie des Menschen, Ergebn. d. inn. Med. u. Kinderh. **10**:531, 1913.

14. Veil, W. H.: Physiologie und Pathologie des Wasseraushaltes, Ergebn. d. inn. Med. u. Kinderh. **23**:648, 1923.

by a rapid disappearance of the excessive water and sodium chloride into the tissues.

Cohnheim [15] recognized the frequent occurrence of edema in hydremic patients, but was of the opinion that hydremia is not a cause of edema, and that hydremic plethora is not the cause of generalized edema of the type characteristic of renal disease. Volhard [16] believed that hydremia leads to diuresis, and that if diuresis is impossible the hydremia continues, but that this alone is not sufficient to cause edema. Volhard and Fahr [9] thought that Keller's finding of concentrated blood in the early stage of nephrosis shows that edema is not caused by poor elimination of water by the kidneys, but that poor elimination of water is to be considered a consequence of scarcity of water in the blood. Nonnenbruch [10] agreed with Volhard that the finding of concentrated blood in renal edema indicates an extrarenal cause of the edema, but said that edema of extrarenal origin does not necessarily produce concentrated blood.

The results of the determination of blood and plasma volumes as a means of indicating whether the blood is diluted or concentrated in edema of the renal type also present considerable disagreement. Linder, Lundsgaard, Van Slyke and Stillman,[17] in two cases of glomerulonephritis of the nephrotic type, in one case of acute nephrosis and in one case of chronic nephrosis, in which the blood plasma volume was determined before, during and after disappearance of extensive edema, found the plasma volume to be uninfluenced by the presence of edema or else actually diminished with the anasarca extreme. In two of these cases, a moderate but definite increase in the plasma volume occurred as the edema disappeared. Darrow and Buckman [18] found a diminished plasma volume in three cases of renal edema in children and in one case in an adult. In two of these cases diagnosed as nephrosis, both in children, the plasma volume returned to normal with the disappearance of the edema. Rusznyák [19] found the blood volume diminished, with nor-

15. Cohnheim, J.: Lectures on General Pathology (A Handbook for Practitioners and Students), translated from the second German edition by Alexander B. McKee, London, The New Sydenham Society, 1889-1890, sect. 1, pp. 452 to 460.

16. Volhard, F.: Die doppelseitigen hämatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918, p. 100.

17. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Protein in Nephritis, J. Exper. Med. **39**:921, 1924.

18. Darrow, D. C., and Buckman, T. E.: The Volume of the Blood: II. The Volume of the Blood and Concentration of Crystalloids and Electrolytes in Dehydration and Edema, Am. J. Dis. Child. **36**:248 (Aug.) 1928.

19. Rusznyák, S.: Untersuchungen zur Frage der Gesamtblutmenge des Menschen unter normalen und pathologischen Verhältnissen: II. Nierenkrankheiten und Hypertonien, Deutsches Arch. f. klin. Med. **158**:98, 1927.

mal or slightly increased plasma volume, in three cases of acute glomerular nephritis, two of these with edema, and in one case of subacute glomerular nephritis with mild edema. All of these workers determined the blood volume by means of the dye method.

Using an infusion method of determining blood volume, Plesch,[20] in 1909, found the blood volume percentage of body weight less than one half of normal in a case of renal edema of extreme degree. In 1922, with the carbon monoxide method, he found a low blood volume in one case of renal edema, and a blood volume of about normal, which increased as edema subsided, in two other cases. Waterfield,[21] by a carbon monoxide method, determined the blood volume in five adults with renal edema. His results indicated that the blood volume is low with edema at its height, increases as edema disappears, and may fall again if edema subsequently reappears. In cases without anemia, the changes are of the plasma volume only.

On the other hand, Bock [22] found the plasma volume per kilogram of body weight normal and constant in nephritis with edema; and Brown and Rowntree [23] found normal values for plasma and blood volume in cases of renal edema uncomplicated by anemia. The latter authors,[23a] in cases of nephrosis with diminished hemoglobin and cell values, found the blood and plasma volume definitely increased, but stated that there was no good evidence to indicate that a dilution phenomenon had occurred. Bock, and Brown and Rowntree determined the blood volume by a dye method.

The concentration of the proteins in the plasma in edema of the renal type has been the subject of considerable interest and study, especially since Epstein,[3] in 1917, adapted Starling's theory concerning the influence of the serum proteins on the exchange of water between the blood and the tissues, to explain, on the basis of a low protein concentration in the plasma, the production of the noncardiac edema of chronic parenchymatous nephritis. Starling,[24] in 1896, reported experiments which indicate that the osmotic pressure due to the serum protein of the normal blood approximates capillary blood pressure, and suggested that

20. Plesch, J.: Untersuchungen über die Physiologie und Pathologie der Blutmenge, Ztschr. f. klin. Med. **93**:241, 1922; Hämodynamische Studien, Ztschr. f. exper. Path. u. Therap. **6**:380, 1909.

21. Waterfield, R. L.: Changes in Blood Volume in Patients with Edema of Renal Origin, J. Clin. Investigation **9**:589, 1931.

22. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83 (Jan.) 1921.

23. (*a*) Brown, G. E., and Rowntree, L. G.: Blood Volume in Edema of Glomerular Nephritis and Nephrosis, Arch. Int. Med. **41**:44 (Jan.) 1928; (*b*) The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, ibid. **35**:129 (Jan.) 1925.

24. Starling, E. H.: On the Absorption of Fluids from Connective Tissue Spaces, J. Physiol. **19**:312, 1895-1896.

this osmotic pressure tends to counteract the capillary pressure, thus maintaining a balance between filtration of fluids from the blood vessels into the tissues and absorption of fluids from the tissues into the blood.

There are many reports of the finding of a low concentration of protein in the serum and plasma in edema of the renal type. Bright,[25] in 1827, referred to the finding by Bostock of low serum protein in patients with heavy proteinuria, and, in 1831, to Babbington's finding of 5 per cent of albumin in the serum of a patient with albuminuria and anasarca of two years' standing. Csatáry,[26] in 1891, noted that the serum albumin was more affected than the globulin, which sometimes caused the albumin-globulin ratio to fall below 1; and Erben,[27] in 1905, emphasized the presence of a low or reversed albumin-globulin ratio in parenchymatous nephritis. Epstein,[28] in 1912, by chemical methods, found a low total serum protein with a very low albumin-globulin ratio in two patients with parenchymatous nephritis, and in subsequent papers he has emphasized the presence of a low serum protein in active nephrosis.

The presence of a low concentration of protein in the serum and plasma in the nephrotic type of edema has been confirmed by many workers, including Kollert;[29] Linder, Lundsgaard and Van Slyke;[30] Fahr and Swanson;[31] Moore and Van Slyke;[32] Van Slyke and associates;[5] Clausen;[33] Fodor and Fischer;[34] Peters and associates;[35]

25. Bright, Richard: Reports of Medical Cases, London, Longman, 1827-1831, vols. 1 and 2.

26. Csatáry, A.: Ueber Globulinurie, Deutsches Arch. f. klin. Med. **48**:358, 1891.

27. Erben, F.: Studien über Nephritis, Ztschr. f. klin. Med. **57**:39, 1905.

28. Epstein, A. A.: A Contribution to the Study of the Chemistry of Blood Serum, J. Exper. Med. **16**:719, 1912.

29. Kollert, V.: Ueber das Wesen der Nephrosen, Ztschr. f. klin. Med. **97**: 287, 1923.

30. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Protein in Nephritis, J. Exper. Med. **39**:887, 1924.

31. Fahr, G., and Swanson, W. W.: The Quantities of Serum, Albumin, Globulin, and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies, Arch. Int. Med. **38**:510 (Dec.) 1926.

32. Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

33. Clausen, S. W.: Parenchymatous Nephritis: I. As a General Systemic Disease, Am. J. Dis. Child. **29**:581 (May) 1925; II. Infection of Paranasal Sinuses as Etiology, ibid. **29**:587 (May) 1925; III. The Surface Tension of the Blood Serum, ibid. **29**:594 (May) 1925.

34. Fodor, A., and Fischer, G. H.: Chemische und kolloidchemische Untersuchung des Blutserums und der Oedemflüssigkeit bei Oedematösen: I. Beitrag zur Theorie des Oedems, Ztschr. f. d. ges. exper. Med. **29**:465, 1922.

35. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P. N., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: IV. Serum Proteins in Nephritic Edema, J. Clin. Investigation **10**:941, 1931.

Schwarz and Kohn;[36] Blackfan and Hamilton;[37] Calvin and Goldberg;[38] Schlutz, Swanson and Ziegler,[39] and Wolbach and Blackfan.[40] The last five studies were principally in children. In most instances, when albumin and globulin were determined separately, the decrease in total protein was due to a decrease in albumin, and not infrequently the globulins were increased. Kollert [29] pointed out the high fibrinogen content in the plasma of nephrotic patients.

Clausen,[33] from the determinations of the serum proteins in nine cases of parenchymatous nephritis, concluded that edema in parenchymatous nephritis is correlated with low serum protein.

Peters and his associates [35] determined the total proteins of the serum one hundred and seventy-nine times in twenty-one patients with nephrosis or nephrotic types of nephritis and the albumin and globulin fractions separately in one hundred and eighteen instances in fifteen patients. They found edema almost invariably present when the total serum protein was below 4 per cent, but in only three instances, in two patients with circulatory failure, when the total protein was above 5 per cent. Edema was found in every instance when the serum albumin was below 2 per cent, and in only one instance (in a case of heart block) when it exceeded 2.75 per cent. They stated that with the total protein of the serum between 4 and 5 per cent, edema can usually be eliminated by proper treatment, but that when it is below 4 per cent treatment is usualy ineffectual.

Barker and Kirk [41] found that when the serum albumin in nephritic patients fell to about 1 per cent, edema appeared, and that it decreased shortly after the albumin increased above 1 per cent.

Govaerts [42] found the osmotic pressure of the serum protein low

36. Schwarz, H., and Kohn, J. L.: Studies of Nephritis in Children: I. Nephrosis, Am. J. Dis. Child. **24**:125 (Aug.) 1922.

37. Blackfan, K. D., and Hamilton, B.: A Study of the Inorganic Constituents of the Serum in Children with Acute Nephritis, Bull. Johns Hopkins Hosp. **41**:322, 1927.

38. Calvin, J. K., and Goldberg, A. H.: Plasma Proteins and Edema: Their Relationship in a Group of Children Presenting the Nephrotic Syndrome, Am. J. Dis. Child. **42**:314 (Aug.) 1931.

39. Schlutz, F. W.; Swanson, W. W., and Ziegler, M. R.: The Distribution of the Globulin and Albumin Fractions in the Blood and in the Urine in Nephrosis, Am. J. Dis. Child. **36**:756 (Oct.) 1928.

40. Wolbach, S. B., and Blackfan, K. D.: Clinical and Pathological Studies on So-Called Tubular Nephritis (Nephrosis), Am. J. M. Sc. **180**:453 (Oct.) 1930.

41. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

42. (*a*) Govaerts, P.: Influence du rapport albumines-globulines sur la pression osmotique des protéines du serum, Comp. rend. Soc. de biol. **93**:441, 1925; (*b*) Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedèmes, Bull. de l'Acad. roy. de méd. de Belgique **7**:356, 1927.

in nephritic patients with edema. His investigations showed that the albumin fraction exerts approximately four times as great osmotic pressure per gram as the globulin, and that a direct relationship exists between serum osmotic pressures and albumin-globulin ratios.

While the association of a low concentration of the plasma protein with edema of the nephrotic type has been reported by many investigators, some of these have also reported observations which do not seem in keeping with the theory that the formation of the edema is the result of the low concentration of the plasma protein. Schwarz and Kohn,[30] in discussing the cause of edema in nephrosis, referred to a child with a general anasarca and with serum protein of 4.2 per cent who lost 29 pounds (13.2 Kg.) of weight within a week, with disappearance of all manifest edema without change in the blood protein concentration, and said: "It would not appear, therefore, that the reduction in the protein content of the blood is a great factor." Linder, Lundsgaard and Van Slyke [30] stated that with disappearance of edema in their cases the plasma protein concentration was usually increased, but that this was not constant, and concentrations of 4.5 per cent or less were compatible with persistent absence of edema. In discussing the hypothesis that the edema of nephritis is the result of decreased osmotic pressure of the plasma due to low concentration of protein, these authors said: "If this were true it is probable that the lowest protein concentration in the plasma would be found during the stage of increasing and fully developed edema, and that the first sign of a change for the better would be a rise in the osmotic pressure consequent upon an increase in the plasma protein," and that in the results reported by them, "no such close relationship appears." Fahr and Swanson [31] are inclined to believe that though a reduction in the plasma protein tends to slow up the output of water somewhat, it is only a minor factor in the formation of edema. In one of their cases of chronic nephrosis with total plasma proteins of 75 per cent and albumin less than 50 per cent of mean normal, the patient excreted 1,350 cc. of urine in four hours after a fluid intake of 1,500 cc. In several cases of glomerulonephritis, a low plasma protein with markedly low albumin fraction was present when diuresis had set in and edema had disappeared. Moore and Van Slyke [32] studied the relationship of the plasma protein concentration to the presence or absence of edema in seventy-five cases of nephritis, and said: ". . . the main and constant factor in producing the tendency toward non-cardiac edema in nephritis is plasma protein deficit." Yet, they pointed out that this is not the only factor in determining the occurrence and degree of edema. They stated that patients with low plasma protein may become comparatively, and sometimes entirely, edema-free on a salt-free regimen, and referred to "an unknown physiological factor, which in cases where occurrence or non-occurrence of edema is in the balance, may determine whether edema will occur or not." Van

Slyke and associates [5] found that the tendency to noncardiac edema in nephritis (except in the first weeks of acute nephritis) and in nephrosis approximately paralleled the fall in albumin content of the plasma. They expressed the belief that there are other factors, however, which may resist or reenforce the hydropigenous effect of a deficit of plasma protein, and that with plasma proteins near the level at which their deficit usually produces edema these other modifying factors may cause edema to appear or disappear. They mentioned salt intake as such a factor, and said that with the tendency to edema barely under control, it may appear after infection or operation, and that in some instances fever and in others vomiting seem to make it disappear. Calvin and Goldberg [38] said that edema often appears and disappears more rapidly than do the changes in the blood proteins, and expressed the belief that while the low serum albumin is an important underlying predisposing factor, it cannot entirely account for the sudden changes in the edema, and that the relationship is not a simple one of cause and effect. They refer to some "trigger" mechanism which suddenly causes retention of water, or diuresis, resulting in the typical "cyclic" edema of the nephrotic syndrome in children.

The lack of agreement regarding the water content of the blood in edema of the renal type and the importance of this knowledge to the theories of the cause of the edema make further study on this subject seem worth while. It seems especially desirable to have more information on the changes of the water content of the blood coincident with changes in the course of the edema. We have tried, therefore, to obtain data through the complete cycle of attacks of edema and, especially, at short intervals when the edema was changing from one phase to another.

Although we made no determinations of the absolute volume of plasma or blood, our data on changes in the relative volume of plasma, when considered in relation to the red blood cell and hemoglobin values, and the figures for the total blood solids seem to justify the drawing of conclusions concerning changes in the absolute volume of the plasma. This is especially true of nephrosis, in which rapidly progressing anemia is uncommon and the absolute volume of cells, therefore, is not subject to rapid change from that cause.

The coincidence of edema of the nephrotic type and a low concentration of protein in the plasma, mainly due to decrease in the albumin fraction, is established beyond reasonable doubt by published data. That the low protein concentration in the plasma is the cause of the edema is yet to be proved.

We have attempted to secure further data on whether or not, in the individual patient, decrease and increase in the plasma protein concentration precede respectively increase and decrease, or appearance and disappearance, of the edema with sufficient regularity to indicate a cause and effect relationship. It was thought, also, that a study of the

relation of changes in the concentration of protein in the plasma to changes in the water content of the blood during the cycle of edema might furnish information concerning the influence of plasma protein concentration on the movement of water between the blood stream and the tissues, such as might be expected from consideration of the effect of the proteins on osmotic pressure, if the concentration of proteins in the plasma is important to the development and subsidence of edema.

PROCEDURE AND METHODS

Blood was taken from an antecubital vein at about 10:30 a. m., approximately three hours after breakfast. Care was taken to prevent, so far as possible, prolonged stasis.[43]

In each case, when practicable, the whole blood solids, the relative volumes of cells and plasma, the specific gravity and viscosity of whole blood, the hemoglobin content, the number of red blood cells and the percentage of the protein in the plasma, and in some cases, of the plasma fibrinogen, globulin and albumin, separately, were determined. The nonprotein nitrogen and cholesterol content of the blood were determined as aids to diagnosis.

Total solids of whole blood and of plasma were determined in duplicate by the method described by Myers.[44] In the case of plasma solids, a correction was made for the sodium oxalate that had been added to the blood to prevent coagulation. With few exceptions, the duplicates checked within 0.2 on the percentages of the total solids in the whole blood and in the plasma figure.

Plasma proteins, total and fractional, were determined in case 1, and in a few isolated determinations recorded in chart 9, by the method of Wu.[45] In all the other cases, the method described by Hawk and Bergeim[46] was used. This combines the method of Howe[47] for the separation of the globulins from the albumin, and the separation of the fibrinogen from the other proteins, with the

43. The observations of Rowe (*a*, The Effect of Venous Stasis on the Proteins of Human Blood Serum, J. Lab. & Clin. Med. **1**:485, 1915-1916), Peters, Eisenman and Bulger (*b*, The Plasma Proteins in Relation to Blood Hydration in Normal Individuals and in Miscellaneous Conditions, J. Clin. Investigation **1**:435, 1925) and Plass and Rourke (*c*, The Effect of Venous Stasis on the Proteins of Blood Plasma and on the Rate of Sedimentation of the Red Blood Corpuscles, J. Lab. & Clin. Med. **12**:735, 1927) indicate that venous stasis of five minutes' duration or more may cause a considerable increase in the relative cell volume and red blood cell count, and in the hemoglobin and plasma protein concentrations. It seems possible that these effects of stasis may be even greater in cases of renal edema with low plasma protein concentration.

44. Myers, Victor C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 160.

45. Wu, H.: A New Colorimetric Method for the Determination of Plasma Proteins, J. Biol. Chem. **51**:33, 1922.

46. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1927.

47. Howe, P. E.: The Use of Sodium Sulphate as the Globulin Precipitant in the Determination of Proteins in the Blood, J. Biol. Chem. **49**:93, 1921; The Determination of Proteins in Blood—A Micro Method, ibid. **49**:109, 1921.

method of Koch and McMeekin[48] for the nitrogen determination. The plasma used for these determinations was obtained from blood oxalated in the concentration of from 30 to 50 mg. of sodium oxalate per 10 cc. of blood. Because of the cell shrinkage and consequent increase in relative plasma volume brought about by the hypertonicity in the blood specimens, our figures for protein must be considered to be slightly lower than their absolute values, and since the oxalation was not carried out in a perfectly constant concentration, it must also be considered that in successive protein determinations in a given case there may be relative errors to the extreme (rarely, though possibly) of 0.3 in the figures for the percentage of total protein in the plasma.

Nonprotein nitrogen was determined by the method of Folin and Wu[49] with the Haden[50] modification for preparing the protein-free filtrate.

Cholesterol was determined in the earlier cases (cases 1, 2, 3-I, 3-II, 5, 6 and 7) by the method of Bloor[51]. The last three determinations in case 3-II and all determinations in case 4 were made by the method of Leiboff.[52]

Specific gravity was determined with bottles of the Gay-Lussac type of 1 cc. capacity. Control experiments done with water with a procedure like that used for the blood indicated that our average error in the figure for specific gravity should be considered as 0.001.

Viscosity was determined with a Hess[53] viscosimeter. The method is fully described by Austrian.[54]

Relative cell and plasma volumes were determined in duplicate by a method similar to that employed by Capps.[55] Duplicate tubes of about 0.5 mm. bore and about 5 cm. length, graduated in hundredths, were filled with the fresh blood, without any anticoagulant, and were immediately centrifugated at a minimum speed of 10,000 revolutions per minute, for five minutes. The percentages were read, and then centrifugation was continued for two minutes longer, and readings made again. Usually the readings were constant, but if there was any change at the second reading, the centrifugation was again continued for two minutes. The duplicate readings of the relative cell volume in percentage of blood checked each other within 2 and most often within 1. Three control experiments were done, one on human blood and two on sheep's blood, to compare the readings on fresh blood

48. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, J. Am. Chem. Soc. **46**:2066, 1924.

49. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

50. Haden, R. L.: A Modification of the Folin-Wu Method for Making Protein-Free Blood Filtrate, J. Biol. Chem. **56**:469, 1923.

51. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227, 1916; ibid. **29**:437, 1917.

52. Leiboff, S. L.: A Simplified Method for Cholesterol Determination in Blood, J. Biol. Chem. **61**:177, 1924; Modifications in the Method for the Determination of Cholesterol in Blood, J. Lab. & Clin. Med. **15**:776, 1930.

53. Hess, W.: Die Viskosität des Blutes bei Gesunden, Deutsches Arch. f. klin. Med. **94**:404, 1908.

54. Austrian, C. R.: The Viscosity of the Blood in Health and Disease, Bull. Johns Hopkins Hosp. **22**:9, 1911.

55. Capps, J. A.: A Study of Volume Index: Observations upon the Volume of Erythrocytes in Various Disease Conditions, J. M. Research **5**:367, 1903-1904.

with those on the same specimen heparinized. In every experiment the value for cell volume in the heparinized sample was found to be less than 1 lower than the value in the fresh sample. This would indicate that any error due to coagulation, in our method, may be considered to be included in an average error of 1 for the relative volume of the cells or of the plasma expressed in percentage of the whole blood.

Hemoglobin was determined in the earlier cases (1, 2, 3-I, 5, 6 and 7) by the acid hematin method of Haden.[56] The standard acid hematin solution was made by the oxygen capacity method of Van Slyke and Stadie.[57] In the later cases (3-II and 4), the Newcomer [58] method was used. The glass disk used was standardized by the Bausch and Lomb Optical Company and released by them in February, 1930.

Single specimens of urine, taken at the time of the withdrawal of specimens of blood, were examined for albumin, blood cells and casts. Records of the daily (12 midnight to 12 midnight) quantity of fluids taken and urine excreted were kept by the nursing staff. Daily weights of the patients at about 8:30 a. m., the degree of pitting of the arm and leg and the results of the intradermal salt solution test [59] were recorded as evidence of the degree of edema and its course.

As might be expected, it was exceptional that a patient was under observation at the onset of the edema, and in the two instances in which this occurred the exact point of the beginning of the edema was not sharply defined. Likewise, it was usually impossible to determine the exact point of disappearance of the last trace of edema: a slight or questionable pitting on pressure over the shin frequently persisted for some time after diuresis seemed to have ended. The intradermal salt solution test was helpful at times in arriving at a conclusion concerning the state of the edema in such instances. On the other hand, the onset of diuresis was in most instances rather well defined and seemed to us an unmistakable sign that the factor or factors responsible for the development, or at least the continuance, of the edema were no longer active or were rendered ineffective by a new factor. A somewhat less definite but earlier evidence of improvement in some of our cases was the lessening of edema of the arm, as shown by lessening of pitting and lengthening of the disappearance time for intradermally injected salt solution in that region. This was seen on several occasions in the stationary phase of edema preceding diuresis.

CLINICAL MATERIAL

This report includes data from six patients with renal edema, each studied in both the advancing and the subsiding phase of an acute

56. Haden, R. L.: A Method for the Determination of Hemoglobin, J. Lab. & Clin. Med. **8**:411, 1922-1923.

57. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1, 1921.

58. Newcomer, H. S.: Absorption Spectra of Acid Hematin, Oxyhemoglobin, and Carbon Monoxide Hemoglobin. A New Hemoglobinometer, J. Biol. Chem. **37**:465, 1919.

59. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293 (July 28) 1923. Aldrich, C. A., and McClure, W. B.: The Intradermal Salt Solution Test: II. Its Prognostic Value in Nephritis with Generalized Edema, J. A. M. A. **82**:1425 (May 3) 1924.

attack of edema, and from one patient (case 7) studied only during a rather irregularly subsiding phase.[60]

For one patient the data from two attacks of edema (cases 3 I and 3 II) are presented. So far as could be judged, there was no anemia in any case at the time of the first determination. Data from sixteen additional cases of renal edema, not presented in detail because they were not

Data on

No.	Date	Age, Years	Sex	Diagnosis and Condition at Time of Test	Urine, Single Specimen about 11 a.m.						
						Microscopic Low Power Field					
						Centrifugated			Uncentrifugated		
					Albumin	Red Blood Cells	White Blood Cells	Casts	Red Blood Cells	White Blood Cells	Casts
1	3/28/28	11 9/12	F	Deformities of legs resulting from poliomyelitis 10½ years before; otherwise considered to be normal	Trace	0	Innumerable	Occasional granular	0	4-6	0
2	4/26/29	9 5/12	M	Deformity of right leg resulting from poliomyelitis 7 years before; otherwise considered to be normal	0	0	0	0	0	0	0
3	12/3/28	9 2/12	F	Congenital dislocation of left hip; otherwise considered to be normal	0	0	50-100	0	0	5-10	0
4	1/14/29	8 8/12	F	Congenital dislocation of both hips; now not in cast; otherwise considered to be normal	0	0	Occasional	0	0	0	0
	2/4/29	8 8/12			0	0	30-50	0	0	Occasional	0
5	7/5/29	8 2/12	F	Partial paralysis of both legs resulting from poliomyelitis about 5 years before; otherwise considered to be normal	0	0	30-40	0	0	3-5	0
6	4/8/29	7 8/12	M	Congenital absence of right fibula; otherwise considered to be normal	0	0	5-10	0	0	0	0
	5/13/29	7 9/12			0	Rare	Occasional	0	0	0	0
7	5/27/29	4 6/12	F	Birth paralysis of left arm (Erbs); otherwise considered to be normal	Trace	0	150-200	0	0	5-10	0
Average											
Number of determinations											
Number of cases											
Normal cases from literature											

* Globulin does not include fibrinogen.

60. A brief report including data from six of these cases was presented before the American Pediatric Society in April, 1931, and a summary published in the Transactions of that society. McClure, W. B.; de Takats, C. B., and Hinman, W. F.: Changes in the Water Content of the Blood During the Course of Edema of Renal Type in Seven Children, Am. J. Dis. Child. **42**:725 (Sept.) 1931; Tr. Am. Pediat. Soc. **43**:62, 1931.

studied in both the advancing and the subsiding phases of edema, or because of the presence of marked anemia, are included in chart 9, which shows the relation between the concentration of protein in the plasma and the degree of edema. Data from seven control cases are presented in the table.

In three of the seven cases with edema which are presented in detail,

Control Cases

Intradermal Salt Solution Test: Disappearance Time, Minutes		Pitting							Total Solids		Plasma Proteins, Gm. per 100 Cc.				Whole Blood	
Arm	Leg	Arm	Leg	Relative Cell, per Cent by Volume	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	Whole Blood Specific Gravity	Whole Blood Viscosity	Per Cent of Whole Blood	Per Cent of Plasma	Total	Globulin*	Albumin	Fibrinogen	Cholesterol, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
60+	—	0	±	—	15.0	5.00	—	4.4	20.0	—	—	—	—	—	—	28.0
60+	60+	0	±	37.0	13.7	5.26	1.049	3.7	18.7	8.45	7.75	2.3	5.05	0.4	250	29.0
60+	60+	0	0	42.5	12.0	5.46	1.051	4.0	19.6	8.45	6.6	—	—	—	220	30.0
60+	60+	0	0	37.5	10.9	4.97	—	3.85	19.2	8.7	6.95	—	—	—	230	30.0
60+	60+	0	0	36.5	11.3	5.38	1.054	3.85	19.0	8.05	7.4	—	—	—	—	28.5
60+	—	0	±	39.5	13.7	5.25	1.050	3.7	19.1	8.4	8.0	—	—	—	220	25.0
60+	60+	0	0	39.0	12.5	—	1.055	3.8	18.85	8.2	7.7	2.3	4.9	0.5	230	30.0
60+	60+	0	0	40.0	12.9	5.56	1.051	3.55	18.8	8.0	6.9	—	—	—	190	28.0
—	60+	0	0	39.0	13.8	4.61	1.052	3.75	19.6	8.35	6.8	1.7	4.75	0.35	220	33.5
.....	.....			38.9	12.9	5.18	1.0526	3.84	19.0	8.4	7.26	2.1	4.9	0.41	224	29.1
.....	.....			8	9	8	7	9	9	8	8	3	3	3	7	9
.....	.....			6	7	7	6	7	7	6	6	3	3	3	6	6
.....	.....			36.5	12.6 to 14.7	5.06	1.0518	3.9	18.95	8.2	7.07	2.22	4.54	0.3	220	27–35

the condition was diagnosed nephrosis; in one of these there was an associated Hodgkin's disease, in which the diagnosis was confirmed at autopsy. In the remaining four of the seven cases, the condition was diagnosed glomerular nephritis with nephrotic syndrome. The seven patients had in common: edema, albuminuria, high blood cholesterol and low plasma protein. The nonprotein nitrogen of the blood was not

above normal at any examination in the cases of nephrosis but a little above normal on several examinations in two cases of glomerular nephritis with nephrotic syndrome. The blood pressure was 115 mm. of mercury at one reading in the case of nephrosis with Hodgkin's disease but normal in the other two cases of nephrosis; it was distinctly above normal in two cases of glomerular nephritis with the nephrotic syndrome. The cases of glomerular nephritis with nephrotic syndrome were differentiated from those of nephrosis particularly on the basis of the finding of more than an occasional red blood cell in the urine.

The drugs administered that might possibly have shortened the course of the edema and brought about diuresis were as follows: In case 2, thyroxin was given from October 13 to November 2 over a period preceding and during diuresis; magnesium sulphate was given throughout the period of study in case 1, from December 5 to December 6 in case 3-II, and irregularly, but only after diuresis had already begun, in case 7.

There was a febrile attack in case 4 during the first three days of diuresis.

At the time of the onset of diuresis, a general diet was being given in cases 1, 2, 5 and 6 (started in case 1, however, only two days before diuresis following a period of low protein, salt-poor diet); low protein, salt-poor diet in case 3-I; low protein, high vitamin, salt-poor diet in case 3-III; high protein, high vitamin diet in case 4, and milk, carbohydrate; salt-poor diet in case 7.

EXCERPTS FROM CLINICAL RECORDS

CASE 1.—*Nephrosis.*

A girl, aged 4 years and 7 months, who was admitted to the hospital on May 8, 1928, had been well until one week before, when puffiness of the eyelids was noticed. Swelling rapidly involved both legs and the sacral region, and the abdomen began to enlarge. During this period she drank a great deal of water, but urinated infrequently and in small quantities. The urine at times was thick and dark. On examination, May 9, there was tonsillitis with an exudate, and a puffy face with swelling of the eyelids and of the arms, legs and abdominal wall. This general edema felt rather firm. There was some movable dulness in the abdomen. The temperature was 99.2 F.[61] on admission and remained within normal range during the period of study. Systolic blood pressure ranged from 72 to 104 mm. of mercury. During our study, cholesterol ranged from 400 to 480 mg., and nonprotein nitrogen from 29 to 33.5 mg. per hundred cubic centimeters of blood.

On May 8, a low protein, salt-poor diet[62] was begun; after May 17, a general diet was given. Water was not restricted.

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61. Rectal temperature.

62. Salt-poor diet means food with salt-free butter and with no salt added in cooking or in serving.

Magnesium sulphate was administered from May 9 to June 1.

The child, improved, went home against advice on June 5. A trace of albumin was found in the urine two days before.

CASE 2.—*Hodgkin's Disease with Nephrosis.*

A boy, aged 6 years and 9 months, was admitted to the hospital on Sept. 13, 1928. He had been admitted in March, 1926, with a diagnosis of Hodgkin's disease. He came to the hospital the second time because of a sudden appearance of edema, five days previously, involving the neck, lower extremities and scrotum. During the stay in the hospital in 1926, the urine, on one examination contained albumin 1 plus, with no casts and no red blood cells. Examination on Sept. 13, 1928, showed, besides the glandular enlargement of Hodgkin's disease, edema with slight redness of the abdominal wall, edema of the scrotum and moderate edema of the legs. On September 15, there was a general edema, especially marked in the right leg, also in the face and scrotum. This edema did not pit easily.

The urine on September 22 showed no albumin; on September 24, the albumin was 1 plus, and on October 3, 4 plus.

The systolic blood pressure was 115 mm. of mercury on September 17. During our study, cholesterol was 380, 310, 390, 380, 310 and 250 mg., and nonprotein nitrogen from 27 to 35 mg., per hundred cubic centimeters of blood.

The temperature on admission was over 105 F.;[61] it rose above 102 F. on September 14, was 103 F. on September 15, became normal on September 16, and continued within normal range until October 1. During October it fluctuated between normal and 100.5 F.; during November it was around 99 and occasionally above 100 F.

On September 13, a general diet was given; on September 14, a light diet, and on September 17, a general diet. Water was not restricted.

On October 13, the administration of thyroxin was begun; it was discontinued on November 2.

The child was admitted to the hospital subsequently on May 13, 1929, for recurrence of general edema four days previously. The urine showed albumin 4 plus. Death occurred on May 17, 1930. Postmortem examination confirmed the diagnosis of nephrosis and Hodgkin's disease.

CASE 3-I.—*Chronic Glomerular Nephritis with Nephrotic Syndrome.*

A boy, aged 5 years and 4 months, was admitted to the hospital for the third time on Feb. 21, 1929. He had first been admitted on Oct. 4, 1927, with general edema and marked albuminuria; he had been admitted a second time on Nov. 6, 1928, for increasing albuminuria. Since being discharged from the hospital on Nov. 13, 1928, albumin had been found in the urine on every visit to the outpatient department. Three days before the present admission the child had had a cold. The urine was reddish on the morning of admission. The boy had seemed drowsy and had had a little headache.

On admission, there was a little swelling about the eyes but none elsewhere. On February 23, there was a slight general edema.

During the period of study the temperature fluctuated somewhat from normal, rising to 100 F.[61] or slightly above on a number of occasions.

The systolic blood pressure varied between 90 and 102 mm. of mercury.

During our study, cholesterol ranged from 420 to 500 mg., and nonprotein nitrogen from 29 to 31.5 mg. per hundred cubic centimeters of blood, with one questionable determination of 48 mg.

On February 21, a low protein diet was given; on February 22, a low protein, salt-poor diet; on February 23, a carbohydrate diet, with no milk, and on February 26, a low protein, salt-poor diet. Water was not restricted.

On February 26, bismuth subcarbonate was administered; it was discontinued on March 3.

CASE 3-II.—The same child as in case 3-I was admitted to the hospital for the fourth time on Nov. 4, 1930. From 1929 until that time there had been several mild attacks of edema at home. Ten days before admission the child had had a cold and sore throat, and a few days later some swelling had appeared about the eyes followed by swelling of the feet and ankles.

On admission there was slight puffiness under the eyes, pitting edema of the legs and albumin 3 plus, but no red blood cells in the urine. In the hospital the temperature fluctuated above and below 99 F.,[61] occasionally rising to 100 F., or slightly above, until January 24, when it was above 102 F. on two examinations. It dropped somewhat during the next two days but fluctuated from about 100 to 101.5 F. until January 30, when it subsided, and it reached normal on January 31. During this study, cholesterol varied from 420 to 610 mg., and nonprotein nitrogen from 28.5 to 39 mg., per hundred cubic centimeters of blood.

On November 4, a general diet was given; on November 6, a low protein, salt-poor diet; on November 10, a general diet, salt-poor, plus high vitamin content; on December 1, a general diet with high vitamin content; on December 5, a salt-poor, low protein, high vitamin diet; on Jan. 3, 1931, a general diet, with high vitamin content; on January 6, a high protein, high vitamin diet; and on January 9, a high protein, salt-poor, high vitamin diet. Water was not restricted.

On December 5, magnesium sulphate was administered; it was discontinued on December 6.

CASE 4.—*Glomerular Nephritis with Nephrotic Syndrome.*

A girl, aged 10 years and 7 months, was admitted to the hospital on May 20, 1931. She had become ill about three months before with pain in the calves of the legs followed within one day by swelling of the feet, legs and ankles. The swelling rapidly increased, involving the thighs, abdomen and face. When she was kept in bed, the legs became less swollen but the buttocks and back more swollen. The swelling of the face and abdomen fluctuated from time to time. From the beginning of the illness the quantity of urine had been small, about a "cupful" a day, and the color yellow, not bloody or dark. For about a year the child had had severe frontal and occipital headaches lasting a day, with, at times, spots and queer lights before the eyes, usually associated with the headaches.

On admission the child did not seem acutely ill; the face was puffy; there was some edema of the neck, back, abdomen and buttocks, with marked edema of the thighs and legs. The heart was normal, and the systolic blood pressure was 84 mm. of mercury. The systolic pressure was 98 on May 28, 98 on June 2, 142 on June 8, 140 on June 11 and 132 on June 13; after that date it varied between 114 and 138, until July 18, when it was 120. From July 27 to September 31, the range was from 104 to 124 mm. of mercury. During our study, cholesterol varied from 420 to 635 mg., and nonprotein nitrogen from 28.5 to 32.5 mg., per hundred cubic centimeters of blood. The temperature was within normal range, except that it reached 100 F.[61] or a little above on several occasions and that there was a period of fever on June 12, 13 and 14, with the temperature as high as 102 F. or a little above each day. During this period of fever the pharynx was very red, the tonsils were hyperemic and swollen, and there was some pain in the throat.

On May 21, a low protein, salt-poor diet [62] was given; on May 22, a high protein, high vitamin diet; after June 19, a high protein, high vitamin, salt-poor diet. Water was not restricted.

Cascara was occasionally given as a laxative. On June 13, a few doses of acetylsalicylic acid were given for pain and fever.

CASE 5.—*Acute Glomerular Nephritis with Nephrotic Syndrome.*

A girl, aged 8 years, was admitted to the hospital on Dec. 16, 1928, for an illness which began one week before with sore throat and "cold," with cough and vomiting. Puffiness of the face was noted, and there was pain in the knees about three or four days before admission. The abdomen had been swollen, and there had been headache, which was less at the time of admission. There was no drowsiness. The urine had been reduced in amount, and a physician found a great deal of albumin.

On admission, there was slight edema of the scalp, moderate edema of both legs and ascites. The urine showed albumin 3 plus with no red blood cells, and the benzidine test was negative. During the period included in our study, the systolic blood pressure varied between 88 and 92 mm. of mercury, and the temperature was below 100 F.,[61] except that it was approximately 100.8 F. on one examination on December 17, and again on December 19. A few red blood cells were found in the urine several weeks after admission. The albumin was rather small in amount, with low specific gravity, and there was good excretion of water. During our study, cholesterol was 450, 450, 470, 400 and 330 mg., and nonprotein nitrogen from 24 to 36.5 mg. per hundred cubic centimeters of blood.

On Dec. 16, 1928, a low protein, salt-poor diet [62] was given; on December 17, a general diet; on Jan. 23, 1929, a general diet, salt-poor, and on February 15, a general diet. Water was not restricted.

No drugs were administered that have any bearing on the study.

CASE 6.—*Chronic Glomerular Nephritis with Nephrotic Syndrome.*

A boy, aged 12 years and 4 months, was admitted to the hospital on Oct. 2, 1928. He had been well until two weeks previously, when swelling of the face, especially about the eyes, appeared. This improved during the week before admission. It had come and gone, having last disappeared on September 30 and having returned in a slight degree on October 1. On admission, there was no edema of the face or of the scrotum.

The blood pressure was 120 systolic and 90 diastolic on October 4, and 110 systolic and 80 diastolic on October 30. In our study cholesterol varied from 370 to 420 mg., and nonprotein nitrogen from 31.5 to 39 mg., per hundred cubic centimeters of blood. The temperature was elevated from admission until October 9, rising to around 104 F.[61] each day from October 3 to 8, inclusive. During this later period there was a diffuse bronchitis. After October 9 the temperature was practically within normal range.

On October 2, a general diet was given, which was continued during the child's entire stay in the hospital. Water was not restricted.

Acetylsalicylic acid was given occasionally.

CASE 7.—*Acute Nephrosis (Acute Tubular Nephritis).*

A girl, aged 3 years and 3 months, was admitted to the hospital on Aug. 26, 1928, as a patient of Dr. George E. Baxter, who referred her to us for special study. One week before admission, the eyelids were seen to be swollen. The next day the abdomen was swollen, and the feet and legs subsequently became swollen. The child had had a slightly sore throat two weeks previous to the

present illness, and again at the time of the onset of the swelling. On admission, the eyelids were swollen sufficiently to close the eyes. There was marked edema of a general type, with the legs and thighs tense and glistening and with some edema of the upper extremities. There was a suggestion of movable dulness in the abdomen.

The urine on August 27 showed 3 plus albumin, but did not show red blood cells or casts. From September 11 to 15, albumin in the urine varied from 7 to 1.5 Gm. per liter by Esbach's test. On September 17, the edema was nearly gone, with no puffiness of the face or swelling of the extremities and with albumin in the urine, 1.7 Gm. per liter. During our study, cholesterol was 590, 580, 540 and 230 mg., and nonprotein nitrogen varied from 28 to 30.5 mg., per hundred cubic centimeters of blood. The systolic blood pressure on August 28 was 88 mm. of mercury.

The temperature was within normal range during the entire period of study, except that it reached 100.2 F.[61] on September 9, 100.4 on September 13 and 100 on September 16. The tonsils and adenoids were removed on September 13, and the child was discharged from the hospital on September 18.

On August 26, the diet consisted of milk not to exceed 1 pint (473 cc.), other fluids not to exceed 1 pint, toast, cereals and other carbohydrates. On August 27, a salt-poor diet[62] was given with potatoes, vegetables and puddings without eggs permitted.

Beginning August 28, magnesium sulphate and magnesia magma were given irregularly.

Subsequent to leaving the hospital, the child was seen by Dr. Baxter on several occasions. On September 22, the albumin in the urine was 1 plus. There was no edema. In October there was more albumin, but on October 29 albumin was absent and the child had no edema. She had a cold in December and again in February, but on neither of these occasions was there any albuminuria. When seen by Dr. Baxter on March 5, 1929, the child was normal.

EXPLANATION OF CHARTS

The first chart for each case is intended especially to show the changes in the water content of the blood in relation to the changes in the course of the edema. Each column represents a specimen of blood with the proportion of the various constituents indicated by the height of the different markings explained in the key. The various elements are measurable in percentage of whole blood by the scale to the left.

The weight curve, when considered in conjunction with the degree of pitting on pressure and the time (minutes) for disappearance of intradermally injected salt solution for the arm (A) and leg (L), given above on the chart, presents a picture of the degree and course of the edema.

Above, also, are given the results of examinations for protein and the number of red blood cells (per low power field in an uncentrifugated specimen) in single specimens of urine collected just after obtaining the specimen of blood.

The values for the red blood cell counts and the hemoglobin and hematocrit determinations are represented graphically below.

The values for viscosity and specific gravity of the whole blood, and for the percentage of water in the whole blood, plasma and cells, are given in figures at the bottom of the chart.

The average values for our control cases and for normal cases from the literature are represented in the two columns to the right, and by the data below these columns.

The normal values from the literature are based on the following data:

Total solids of whole blood: The average of six determinations from Lust [63] and three from Courtney and Fales [64] that fall within our range of ages was taken. This average is 18.95 per cent, which is very close to Brown and Rowntree's [23b] average of 19 per cent for normal adults.

Total solids of plasma: No data for children were found. Hawk and Bergeim [46] gave 8.2 per cent as normal. So, also, did Simon.[65] Brown and Rowntree [23b] gave 8 per cent as the average for fifty normal adults.

Cell solids: No data for children were found. Brown and Rowntree [23b] gave 36 per cent as the average for fifty normal adults.

Plasma protein, total and fractional: For normal children, the total serum proteins were reported as 7.3 per cent by Schwarz and Kohn [36] and as 7.6 per cent by Blackfan and Hamilton,[37] both values having been determined by Kjeldahl methods. However, for normal children we have found no values for plasma proteins, total or fractional, determined by either the Wu or the Howe method. Therefore, we used the following sources to arrive at our "normal values from the literature." By the Wu method: Wu,[45] using plasma, reported for "five normal bloods" averages of 6.94 per cent for total "serum protein," 4.85 per cent for albumin and 2.09 per cent for globulin; Fahr and Swanson [31] reported for nine normal adults averages of 7.2 per cent for total plasma protein, 4.9 per cent for albumin, 2.3 per cent for globulin including fibrinogen and 0.3 per cent for fibrinogen. By the Howe method: Linder, Lundsgaard and Van Slyke [30] reported for "seven normal plasmas" averages of 6.73 per cent for total protein, 4.11 per cent for albumin and 2.61 per cent for globulin including fibrinogen; Moore and Van Slyke [32] reported for heparinized blood of "nine normal subjects" averages of 7.1 per cent for total plasma protein, 4.3 per cent for albumin and 2.8 per cent for globulin including fibrinogen. By converting the foregoing figures into terms of total plasma protein, of plasma albumin and of plasma globulin not including fibrinogen, by use of the figure 0.3 per cent as normal for fibrinogen, and then taking the averages, we obtained the following: total plasma protein, 7.07 per cent; albumin, 4.54 per cent; globulin, 2.22 per cent, and fibrinogen, 0.3 per cent.

Specific gravity of blood: The average of Peiper's [66] figures for eleven normal children (eight boys and three girls) between the ages of 6 and 13 years was

63. Lust, F.: Die Viscosität des Blutes beim gesunden und kranken Säugling, Arch. f. Kinderh. **54**:260, 1910.

64. Courtney, A. M., and Fales, H. L.: Variation in Infants of Total Blood Solids, and the Concentration of Sodium Chloride in Plasma, Am. J. Dis. Child. **14**:202, 1917.

65. Simon, C. E.: A Text Book of Physiological Chemistry, Philadelphia, Lea Brothers & Company, 1901.

66. Peiper, E.: Das specifische Gewicht des menschlichen Blutes, Centralbl. f. klin. Med. **12**:217, 1891.

taken. This average is 1.0518, which falls within the range from 1.050 to 1.052 given by Simon [65] as normal for children. Burton-Opitz [67] does not agree so well, giving 1.058 as normal for children between 2 and 4 years and 1.061 as normal after the sixth year.

Viscosity of blood: The average of six determinations from Lust [63] that fall in our range of ages is 3.965. The average of the figures that Hess [53] obtained for the age range from 1 to 10 years (male, 3.89, and female, 3.8), representing thirty-nine determinations, is 3.845. The final average for these two groups, 3.9, is the figure used.

Relative cell and plasma volumes: The figure used is an average of twenty-seven determinations for twenty-six normal children between the ages of 2.7 and 11 years, from Darrow, Soule and Buckman; [68] this average, 35.4 per cent for relative cell volume, corrected by 3 per cent (in accordance with the statement by two of these authors [18] as to the probable error in their hematocrit determinations due to hypertonicity of the oxalated specimens), is 36.5 per cent.

Hemoglobin: On each chart is recorded Williamson's [69] normal average for the age and sex of the patient in question.

Red blood cell count: Sahli [70] gave minimum and maximum figures from Perlin and Stoose (fourteen children of the ages of 3 years, and of from 11 to 14 years) that average 5,090,000. Sahli also gave four figures from Sorensen (children of from 2 to 10 years) that average 5,030,000. The final average for these two groups, 5,060,000, is used.

The second chart for each case shows the changes in concentration of the plasma proteins in relation to changes in the course of the edema. The albumin, fibrinogen and globulin fractions and the nonprotein solids of the plasma, if determined, are indicated on the columns by the various markings, which are interpreted in the key. The values for these elements may be measured in percentage of plasma by the scale at the immediate left of the first column.

The changes in the relative volume of plasma are indicated by curve *Pl.* and may be read in percentages of whole blood by scale *Pl.* to the left. The state of the edema is indicated as in the first chart for each case, and the average values for the control cases and the normals from the literature are given in the two columns to the right.

There are four charts for case 3, representing two attacks of edema.

CASE 1.—*Nephrosis.*

Edema was first noticed about May 1. There had been no previous attacks of edema.

67. Burton-Opitz, R.: A Text-Book of Physiology, Philadelphia, W. B. Saunders Company, 1920, p. 163.

68. Darrow, D. C.; Soule, H. C., and Buckman, T. E.: Blood Volume in Normal Infants and Children, J. Clin. Investigation **5**:243, 1928.

69. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, a Spectro-Photometric Analysis of Nine Hundred and Nineteen Cases, Arch. Int. Med. **18**: 505 (Oct.) 1916.

70. Sahli, H.: A Treatise on Diagnostic Methods of Examination, ed. 2, edited by N. B. Potter, Philadelphia, W. B. Saunders Company, 1920, p. 763.

In chart 1 *A*, the following points are illustrated: On May 9, with edema increasing, the relative volume of the plasma was markedly below normal; two days later, with edema stationary, it was decidedly higher, and three days before the onset of diuresis it was further increased toward normal. On May 23, with the edema gone, except for a slight pitting of the leg, the relative volume of the plasma had reached normal.

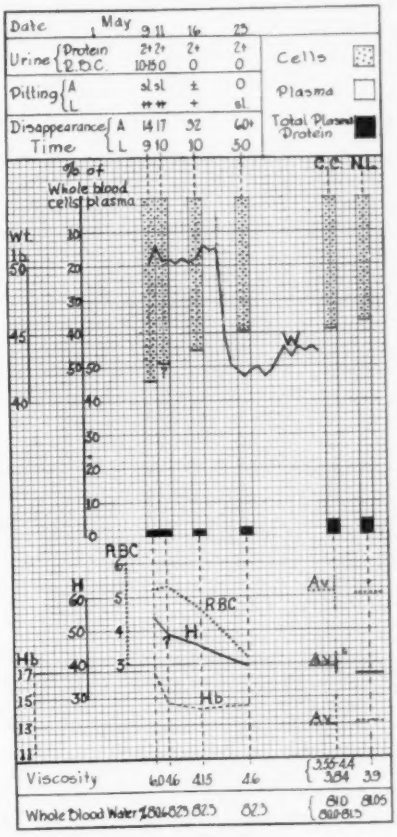

Chart 1 *A*.—Data in case 1. The patient is a girl, aged 4 years and 7 months, with nephrosis. The key to this and charts 1 *B* to 7 *B* follows: *A* indicates arm; *L.*, leg; *sl.*, slight; *tr.*, trace; *occ.*, occasional; *lt.*, little; *C.C.*, control cases; *N.L.*, normal cases from the literature; *W*, weight; *Hb*, hemoglobin; *H*, hematocrit reading; *R B C*, red blood cell count, or red blood cells; *Av*, average, and *Pl.*, plasma. The scale for hemoglobin in the A series of charts is in grams per hundred cubic centimeters of blood; for hematocrit, in per cent, and for red blood cell count, in millions

Here, then, we have a low relative volume of the plasma with edema increasing, which becomes relatively higher with edema stationary, before the onset of diuresis, and reaches normal with loss of edema.

The viscosity of the blood was high during increasing edema, markedly lower with edema becoming stationary, still lower four days before the onset of diuresis, and somewhat higher again at the end of diuresis. It followed rather well the changes in the relative volume of the cells, except that on May 23, with the relative cell volume decreased, the viscosity was increased. At this time, however, the concentration of the total protein in the plasma was higher than at the previous determina-

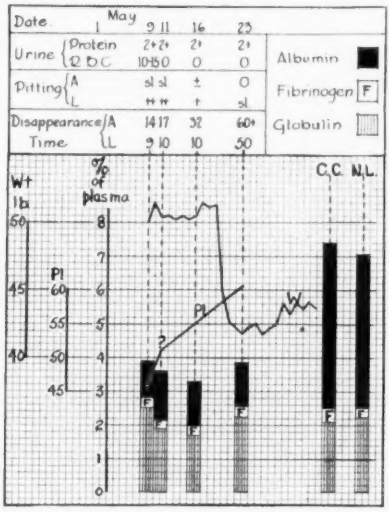

Chart 1 *B*.—Data in case 1. The patient is a girl, aged 4 years and 7 months, with nephrosis. The scale for plasma (headed *Pl*) in the B series of charts is in per cent of whole blood.

tion, and this may have contributed to the increase in viscosity. The time for the disappearance of intradermally injected salt solution for the arm was shortest with advancing edema, somewhat longer with edema stationary on May 11, and definitely longer on May 16 four days preceding diuresis, and normal at the end of diuresis. As is usual in edema, in our experience, the change toward normal of the disappearance time for the leg lagged behind that for the arm. We consider a change in the disappearance time for the arm a much better criterion of the course of the general edema than a change in the time for the leg.

In chart 1 *B*, it is seen that the concentration of the total protein of the plasma was low throughout with the concentration of the albumin

very low and that of the globulin nearly normal or somewhat higher than normal. There was no significant increase in the concentration of the protein in the plasma with diuresis.

If the values for the relative volume of plasma, represented in curve *Pl.* and measured in percentage of whole blood on the scale *Pl.* to the left, are compared with the values for total plasma protein and plasma albumin, it is seen that there is no direct relationship between changes

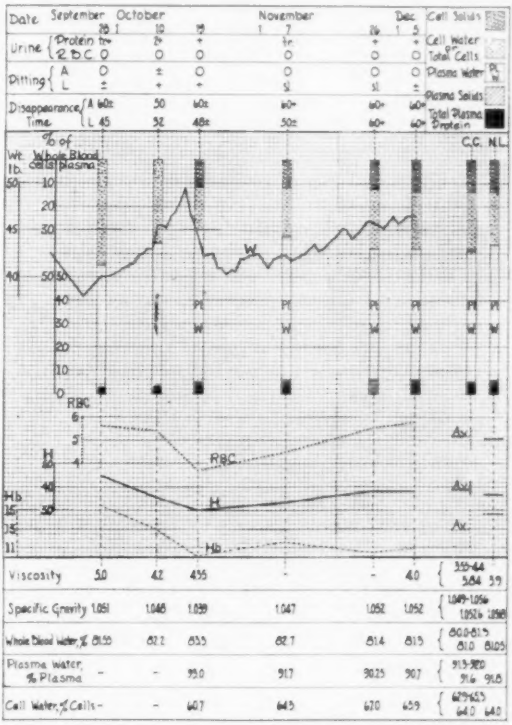

Chart 2 *A*.—Data in case 2. The patient is a boy, aged 6 years and 12 months, with Hodgkin's disease and nephrosis.

in the relative volume of the plasma and changes in the concentration of the plasma proteins.

Case 2.—*Hodgkin's Disease with Nephrosis.*

The patient was admitted to the hospital during his first attack of edema on September 13.

In chart 2 *A*, the following points are illustrated: On September 28, with the present attack of edema (the second one), just beginning, the

relative volume of the plasma was definitely low. Eight days before the onset of diuresis, with the weight remaining unchanged on the next two days, the relative volume of the plasma was considerably higher, and was still higher having a value above normal during diuresis and the loss of edema. The return of the relative volume of the plasma to normal during convalescence was slow.

The increase of the relative volume of the plasma to a value so much above normal at the time of diuresis suggests a moderate anemia or a failure of normal excretion by the kidneys. The latter possibility seems to gain support from the finding of high values for the nonprotein solids of the plasma on November 26 and December 5.

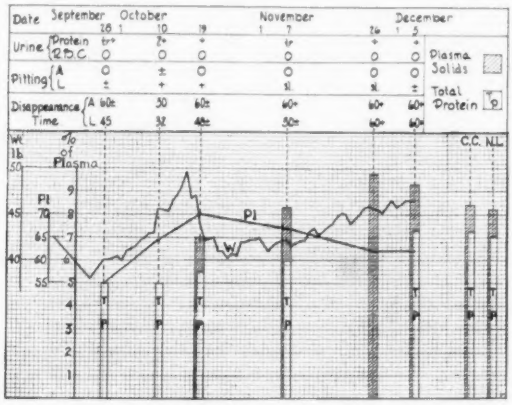

Chart 2 *B*.—Data in case 2. The patient is a boy, aged 6 years and 9 months, with Hodgkin's disease and nephrosis.

The viscosity of the whole blood, like the relative cell volume, was higher than normal with edema developing, and dropped preceding diuresis. With diuresis, however, this relationship of the viscosity to the relative cell volume did not hold, possibly because of the increase in the protein concentration of the plasma.

Chart 2 *B* shows that the concentration of total protein in the plasma was below the critical level for edema of Moore and Van Slyke [71] during

71. Moore and Van Slyke [32] studied the relationship of the total protein and albumin content of the plasma to the presence or absence of edema in seventy-five cases of nephritis. Edema was found in none of the patients with total plasma protein above the range of 5.5 Gm., plus or minus 0.3 Gm. per hundred cubic centimeters, or albumin above the range of 2.5 Gm., plus or minus 0.2 Gm. per hundred cubic centimeters (with one exception probably due to technical error), whereas edema was detectible by ordinary clinical observation in all with figures below these ranges.

the period of development of edema, and within the range of the critical level on the fourth day of diuresis. The values for the non-protein solids of the plasma were high during the convalescent period.

CASE 3-I.—*Chronic Glomerular Nephritis with Nephrotic Syndrome.*

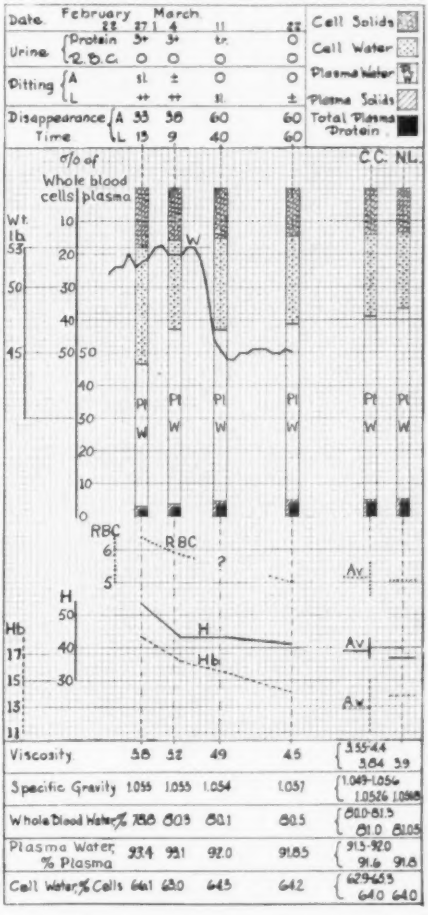
Date
February 22 27
March 1 4 11 22
Urine Protein 3+ 3+ tr. 0
Urine R.B.C. 0 0 0 0
Pitting A sl. ± 0 0
Pitting L ++ ++ sl. ±
Disappearance Time A 33 38 60 60
Disappearance Time L 13 9 40 60
Cell Solids
Cell Water
Plasma Water
Plasma Solids
Total Plasma Protein
% of Whole blood cells plasma
C.C. NL.
Wt. lb.
W
Pl
RBC
H
Hb
Av
Viscosity 5.8 5.2 4.9 4.5 3.55-4.4 3.64 3.9
Specific Gravity 1.055 1.055 1.054 1.057 1.049-1.056 1.0526 1.0568
Whole Blood Water % 78.8 80.3 80.1 80.5 80.0-81.3 81.0 81.05
Plasma Water % Plasma 93.4 93.1 92.0 91.85 91.3-92.0 91.6 91.8
Cell Water % Cells 66.1 63.0 64.3 64.2 62.9-65.3 64.0 64.0

Chart 3-IA.—Data in case 3, series I. The patient is a boy, aged 5 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome.

This patient was studied during two periods of edema which were separated by an interval of about nineteen and a half months. There had been at least one previous attack of edema, in the fall of 1927.

In chart 3-I *A*, representing the first attack studied, a very low relative volume of plasma was present at the first test when the edema was

advancing. This was markedly higher three days before the onset of diuresis and was practically normal ten days after the completion of diuresis.

The viscosity of the blood was high during the development of the edema, somewhat lower before diuresis, and still lower just at the end of diuresis. The changes in the relative volume of cells and viscosity were in the same direction. The disappearance time of intradermally injected salt solution for the arm was longer on March 4 than on February 27.

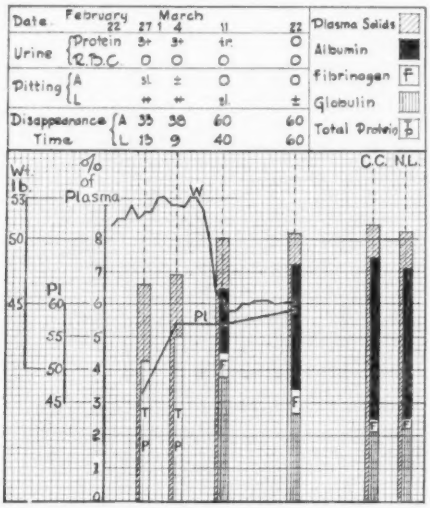

Chart 3-IB.—Data in case 3, series I. The patient is a boy, aged 5 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome.

Chart 3-I *B* shows that the concentration of the proteins of the plasma was low during the period of increase in the edema, a little higher during a stationary period three days before the onset of diuresis, and considerably higher at the end of diuresis, when, however, the albumin fraction was still below the critical level of Moore and Van Slyke for the presence of edema, although the total proteins of the plasma were above the critical level.

A comparison of changes in the relative plasma volume, indicated by curve *Pl.*, with changes in the concentration of total protein in the plasma shows fairly good agreement between the first and second determinations. Subsequently, however, the total protein and albumin concentrations increased considerably with little change in the relative plasma

volume. However, with the plasma proteins near the critical level for edema and with the relative plasma volume nearing normal in the second determination, a further increase of the relative plasma volume probably should not be expected with an increase in the concentration of total protein.

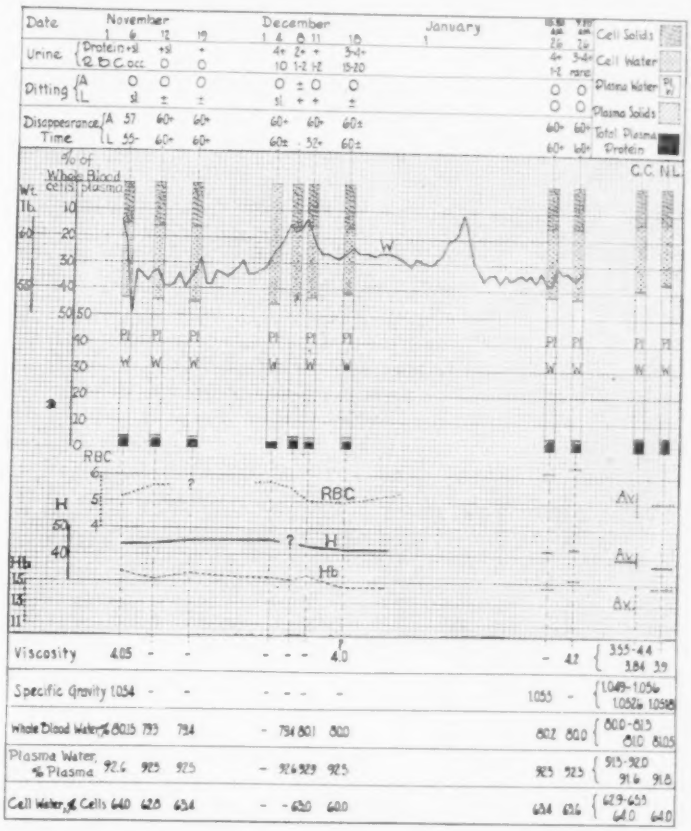

Chart 3-IIA.—Data in case 3, series II. The patient is the same boy as in case 3, series I, now aged 7 years, having chronic glomerular nephritis with nephrotic syndrome. The hemoglobin determination of November 19 was made on an afternoon specimen of blood from the ear.

CASE 3-II.—The second series of determinations were begun during a period of subsiding edema and continued through a mild attack which appeared about a month later.

Chart 3-II *A* shows that on December 4, during a period of advancing edema, the relative volume of the plasma is definitely less than the average for our controls and the average for normal children obtained from the literature. There was a slight increase in the relative volume on December 11 and 18, with the loss of weight and edema. There was no marked diuresis in this attack. The result of the determination on December 8 was discarded because of an accident in the manipulation.

Since the blood for our examinations was usually withdrawn about three hours after breakfast, it seemed desirable to see how this taking of food and fluids might influence the results of our tests. For this pur-

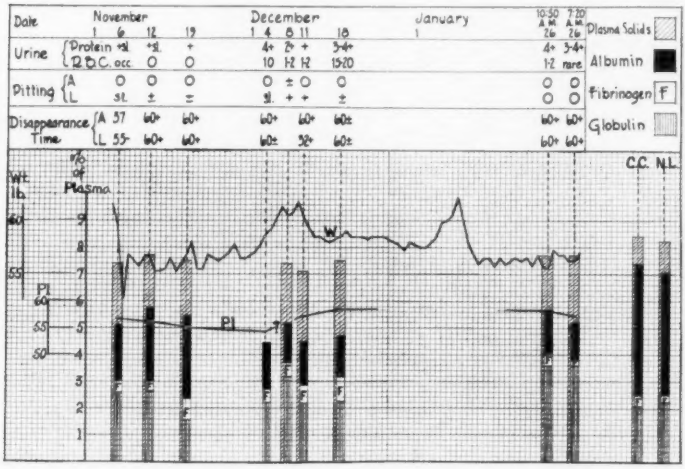

Chart 3-IIB.—Data in case 3, series II. The patient is the same boy as in case 3, series I, now aged 7 years, having chronic glomerular nephritis with nephrotic syndrome.

pose, on January 26, with edema absent, a specimen of blood was taken at 7:20 a. m., when the patient had had no food or fluids since 8 p. m. on the previous day, and another specimen at 10:50 a. m., three and a quarter hours after breakfast. The results of these tests are shown in the two columns and appended data of January 26; the column to the left represents the data of the tests after breakfast. The decrease of 1 per cent in the relative volume of the plasma following breakfast is just within the limits of experimental error.

Chart 3-II *B* illustrates the following points: In the first three determinations, the total protein and the albumin of the plasma were just about at the critical level for edema. During the subsequent mild attack of edema the protein, especially the albumin fraction, was well

below the critical level. There was little change in the level of the albumin fraction throughout this attack of edema; it was lowest when the total protein was highest on December 8, two days before the weight curve began to fall.

The determinations of plasma protein before and after breakfast on January 26 seem to show a little increase in the albumin and fibrinogen fractions following the taking of food and fluids.

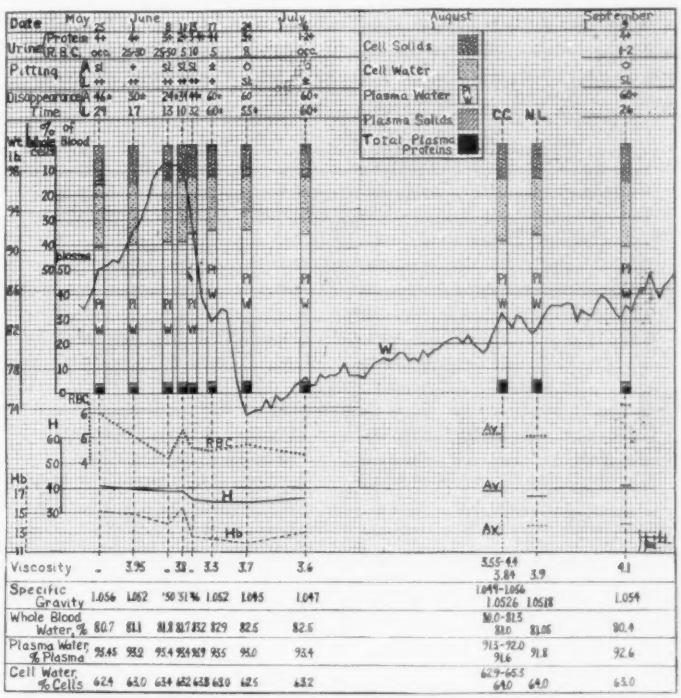

Chart 4A.—Data in case 4. The patient is a girl, aged 10 years and 7 months, having glomerular nephritis with nephrotic syndrome.

The nonprotein solids of the plasma were high throughout, but were highest on December 11 and 18 when the edema was subsiding and when the plasma proteins were low.

CASE 4.—*Glomerular Nephritis with Nephrotic Syndrome.*

This attack of edema, the first one, began about three months before our first examination and fluctuated in degree from time to time.

Chart 4 *A* shows that on May 25, with the edema increasing, the relative volume of the plasma was a little less than the normal average;

at the height of the weight curve, it was just about the normal; and during diuresis and loss of weight, it was a little above normal. On July 6, with the signs of edema gone except for questionable pitting of the leg, the relative volume of the plasma had returned toward normal. But, on September 9, with the disappearance time for the leg and a slight pitting of the leg suggesting a return of edema, the relative volume of the plasma was again a little less than the normal. The viscosity of the blood in a general way varied with changes in the relative cell volume, however, with a modification upward on June 24 when the concentration of the total proteins in the plasma was definitely increased. The disappearance time agreed quite well with the degree of the edema as indicated by pitting on pressure.

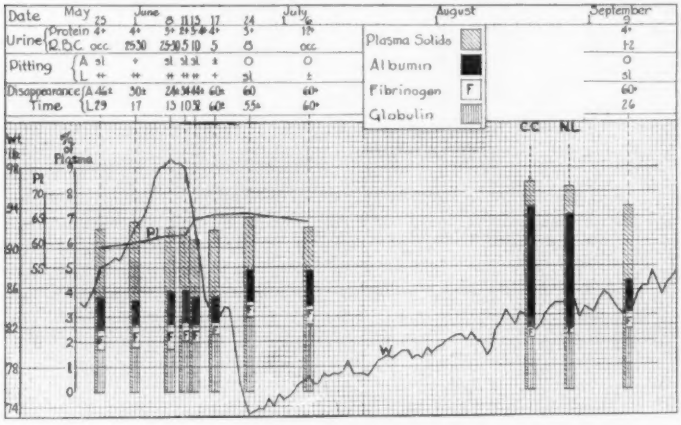

Chart 4B.—Data in case 4. The patient is a girl, aged 10 years and 7 months, having glomerular nephritis with nephrotic syndrome.

Chart 4 *B* shows that the total protein of the plasma and the albumin fraction were both markedly low during the advance of the edema. There was little change in the level of the total protein during diuresis and loss of weight, and the increase at the end of this period on June 24 was principally in the globulin fraction. On July 6, with only a slight or questionable pitting of the leg, together with a normal disappearance time, there was a slight increase in the albumin fraction with no further increase in total protein. This patient went through the entire cycle of edema from the time of our first determination with little change in the concentration of the total protein, and, especially, of the albumin fraction.

A comparison of the changes in curve *Pl.*, representing relative plasma volume, with the changes in the total protein and albumin values,

reveals no correlation. The nonprotein solids of the plasma were high with advancing and with subsiding edema, and were lowest on July 6 with edema practically gone.

CASE 5.—*Acute Glomerular Nephritis with Nephrotic Syndrome.*

A first attack of edema with puffiness of the face was noted about four or five days before the first tests were made.

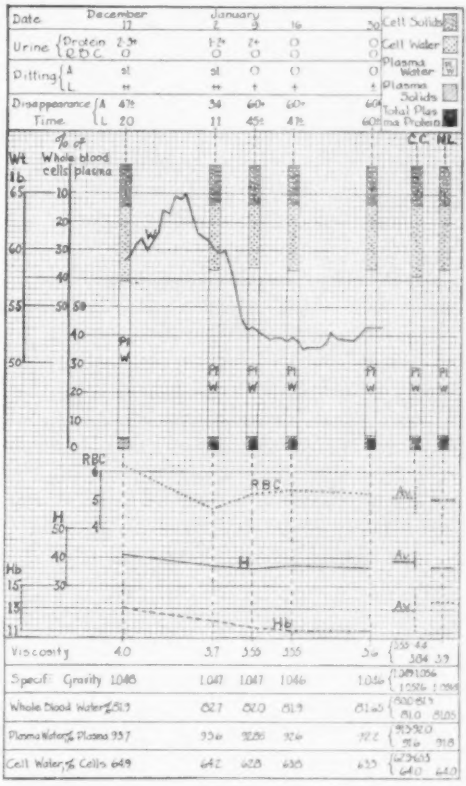
Date
December 12
January 2 3 16 20
Urine Protein 2.3+ 1.5+ 2+ 0 0
RBC 0 0 0 0 0
Pitting A 2+ 2+ 0 0 0
L ++ ++ + + +
Disappearance Time A 47h 34 60+ 60+ 60+
L 20 11 45± 47h 60h
Cell Solids
Cell Water
Plasma Water
Plasma Solids
Total Plasma Protein
% of Whole blood cells plasma
CC. ML.
Wt. lb.
RBC
H
Hb
Viscosity 4.0 3.7 3.59 3.55 3.4
Specif. Gravity 1048 1.047 1.047 1.046 1.046
Whole Blood Water% 81.3 82.1 82.0 81.9 81.45
Plasma Water% Plasma 93.7 93.4 92.86 92.4 92.2
Cell Water% Cells 64.9 64.2 62.8 63.6 63.3

Chart 5A.—Data in case 5. The patient is a girl, aged 8 years, having acute glomerular nephritis with nephrotic syndrome.

Chart 5 *A* shows that the relative volume of the plasma was slightly below the normal average during the development of edema, and slightly above normal during diuresis. The viscosity of the whole blood was normal during the development, and a little below normal during diuresis. The time for disappearance of intradermally injected salt solution agreed quite well with the degree of edema as shown by pitting on pressure.

Chart 5 *B* shows that on January 2, with diuresis well advanced, the total protein of the plasma was low. After this, it increased slowly. The nonprotein solids of the plasma were somewhat high, especially on January 16, when the edema was about gone. They were lower on January 30 with the plasma proteins approaching normal.

CASE 6.—*Chronic Glomerular Nephritis with Nephrotic Syndrome.*

A first attack of edema of rather slight degree, with swelling of the face, was noticed about September 18. The swelling increased and decreased intermittently and finally disappeared on September 30, but recurred on October 1.

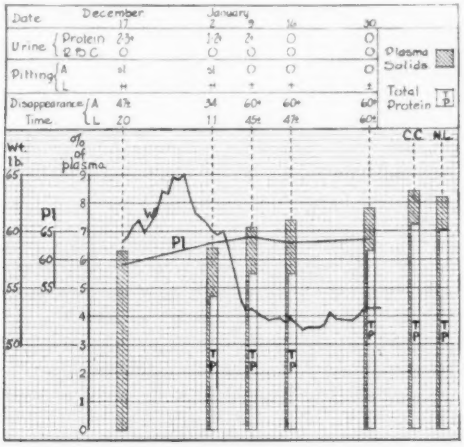

Chart 5B.—Data in case 5. The patient is a girl, aged 8 years, having acute glomerular nephritis with nephrotic syndrome.

Chart 6 *A* shows that on October 5, with the edema still advancing, three days before diuresis, the relative volume of the plasma was less than the normal average. With loss of edema about complete, on October 12, the relative volume of the plasma was about normal. The viscosity, slightly low on the first test, rose above normal with an increase of the relative cell volume, and was slightly higher on October 12 with a decrease of the relative cell volume. On the latter date, however, the concentration of the plasma protein was higher.

Chart 6 *B* shows that the total protein of the plasma was well below the critical level of Moore and Van Slyke [71] for edema when the diuresis was nearly complete; and that it was equally low three weeks later when no definite signs of edema could be made out. There was a high concentration of the nonprotein solids of the plasma during convales-

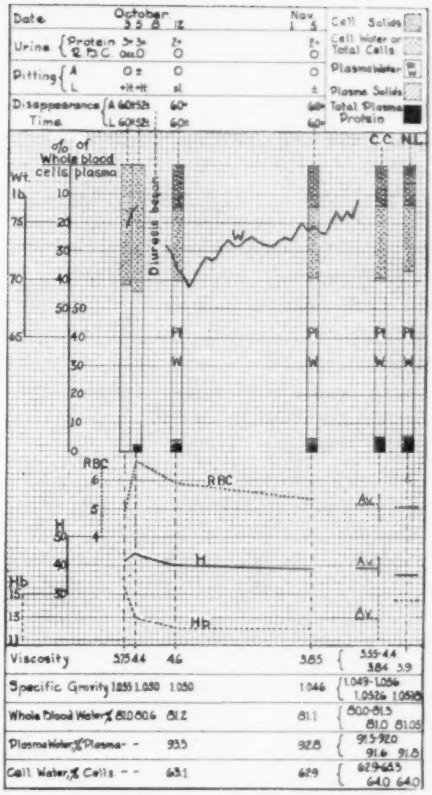

Chart 6A.—Data in case 6. The patient is a boy, aged 12 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome.

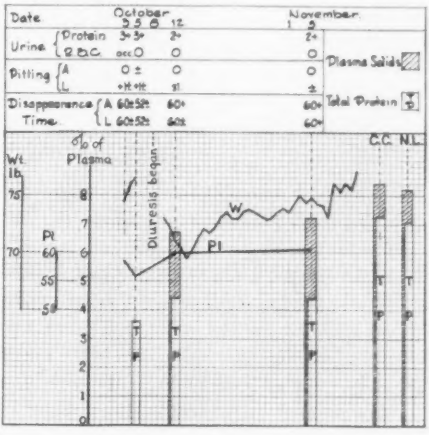

Chart 6B.—Data in case 6. The patient is a boy, aged 12 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome.

cence. Changes in the relative volume of the plasma correlated fairly well with changes in the concentration of the total proteins in the few determinations made.

CASE 7.—*Acute Nephrosis (Acute Tubular Nephritis).*

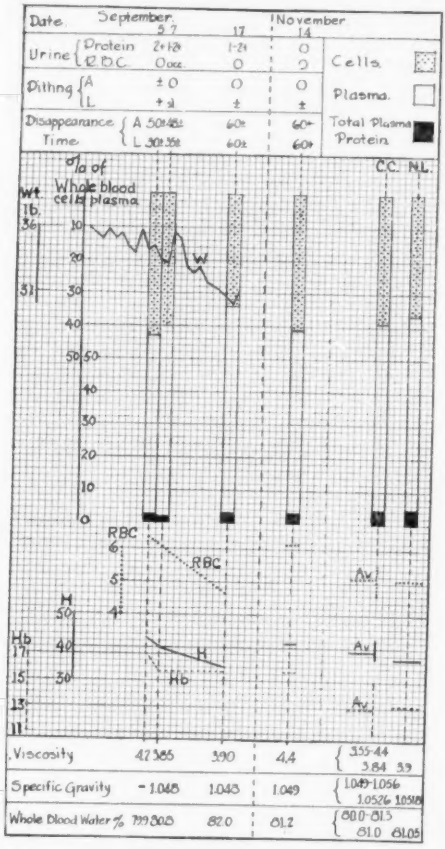

Chart 7A.—Data in case 7. The patient is a girl, aged 3 years and 3 months, with acute nephrosis (acute tubular nephritis).

A first attack of edema of quite moderate grade, which began about August 19, was studied only during an irregularly subsiding phase.

Chart 7*A* shows that on September 5, with the weight fluctuating, the relative volume of the plasma was a little less than the normal average. It was definitely greater than normal at the end of the decline in the edema and about normal two months later when the child was in

good condition. The viscosity and the relative cell volume, in general, changed in the same direction. The disappearance time corresponded rather well with the degree of edema as indicated by pitting.

Chart 7*B* shows that the values for the total protein of the plasma were low, with an abrupt decrease between September 5 and 7 which is unexplained. There was no evident relationship between the changes in the relative volume of the plasma, as indicated by curve *Pl.*, and the changes in the concentration of total protein.

In chart 8 the columns show the relative volumes of plasma and cells in the different phases of edema. The solid black portion of each column represents plasma, and the stippled portion represents cells. The

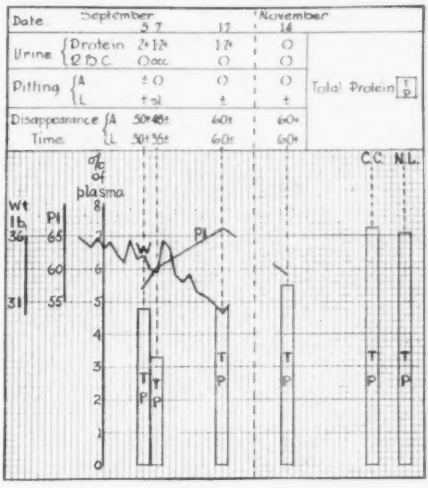

Chart 7B.—Data in case 7. The patient is a girl, aged 3 years and 3 months, with acute nephrosis (acute tubular nephritis).

proportions of plasma and cells may be read in percentages of whole blood by means of the scale to the left. The cases are identified by the numbers at the bottom of the columns. Only cases that were studied in both the advancing and the subsiding phases of edema are included. The multiple width columns represent successive determinations in the same case on different days in the same phase of the edema. For case 3, two series of determinations, one for each of two attacks of edema, are indicated by columns 3-I and 3-II.

The heavy horizontal line crossing the middle of the chart marks the average relative volume of plasma for our controls, which is about 2.4 per cent lower than the average for normal children found in the literature.

It is seen that in every determination in the *developing phase* of edema, i. e., at a time when edema was increasing, the relative volume of the plasma was below the average for the controls; in several instances it was markedly below.

The *stationary phase* of edema is determined by the absence of active changes in the degree of edema as indicated by the weight curve, the figures for the fluid intake and the output of urine, the degree of pitting and the time for disappearance of intradermally injected salt solution considered together. In this phase, the relative volume of the plasma for each case was greater than it was in the previous phase and in one instance exceeded normal.

While the second determination in case 2 did not come at the highest point of the weight curve, yet it is placed in the phase of stationary

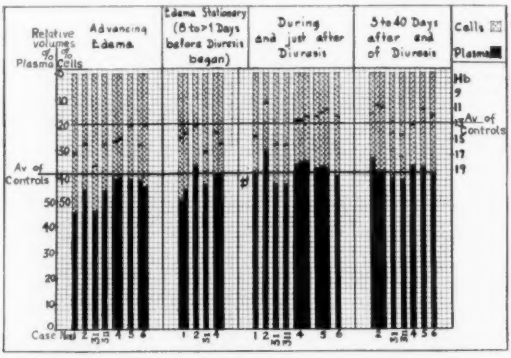

Chart 8.—Relationship of relative plasma volume to phase of edema. The short horizontal lines represent hemoglobin value as measured in grams per hundred cubic centimeters of blood in scale, to right, headed *Hb*. *Av.* indicates average.

edema, since the weight curve remained flat for the next two days following this test.

No determinations were made in the stationary phase in cases 5, 6 and 3-II. In the phase *during and just after diuresis,* the relative volume of the plasma was greater than in the previous phase in three cases, and unchanged in one case, while cases 5 and 3-II, with no determinations in the stationary phase, showed, however, a definitely greater relative volume of the plasma during diuresis than in the developing phase of edema. In two instances in the phase of diuresis and just after diuresis, the relative volume of the plasma was definitely higher than normal. Following diuresis the relative volumes of the plasma tended to attain an equilibrium close to the average normal.

For the purpose of showing to what degree movement of water from cells to plasma and the reverse might account for the variations in the relative volume of plasma, the value for hemoglobin, measurable in grams per hundred cubic centimeters of blood on the scale to the right, is indicated by the short, heavy horizontal line on the stippled portion of each column. The average of the hemoglobin determinations for the controls is indicated by the horizontal line at the level of 13 Gm. per hundred cubic centimeters. It is seen that, in general, the hemoglobin value in the different phases of edema in the same case varies in a direction opposite to that of the changes in the relative volume of plasma and in the same direction as the changes in the relative cell volume, and that these changes in the hemoglobin are of about the same degree as the changes in the relative cell volume. This would not be so if shifting of water between cells and plasma accounted in considerable part for the changes in the relative cell volume, provided the absolute quantity of hemoglobin was not subjected to considerable change.

In chart 9, eighty-two determinations of the total protein and fifty-three of the albumin in the plasma in the various phases of edema of the renal type in twenty-three cases are presented to show the relationship between the concentration of the proteins in the plasma and the presence and the degree of edema. The symbols indicate the degree of edema, as determined by pitting of the arm and leg considered in conjunction with the time for disappearance of intradermally injected salt solution in the same regions at the time of the determination of the plasma proteins. In this classification, if pitting on pressure was questionable and the time for disappearance of intradermally injected salt solution was normal, edema was considered to be absent. The position of the symbol in relation to the scale to the left indicates the value for the total plasma protein, or the plasma albumin, in per cent of plasma. The heavy horizontal lines mark the limits of the critical levels of total protein and albumin in the plasma for the occurrence and nonoccurrence of edema, as determined by Moore and Van Slyke [71] for adults. The data charted to the right of the perpendicular line, both in the total protein and in the albumin group, are from the seven cases presented in detail in this paper. The data to the left of these lines represent determinations in sixteen other cases of the renal type of edema in children not presented in detail for reasons given under the discussion of the clinical material. If we take the open circles and squares as indicating the instances of definite edema, there is only one instance of definite edema in which the total protein of the plasma was above the upper limit of the critical level for edema of Moore and Van Slyke. If we consider edema to be absent in all instances represented by black circles and crosses, there are nine instances of absence of edema with the total protein of the plasma well

below the lower limit of the critical level. On analyzing the graph with respect to the albumin of the plasma similarly, there are no instances of definite edema with the albumin above the upper level of the critical level for edema. There are, however, six instances of absence of edema with the albumin of the plasma below the lower limit of the critical level. The greatest concentration of total protein, and of albumin, with edema present in our cases corresponds quite well with that found by Moore and Van Slyke for adults. The lowest concentration of total protein

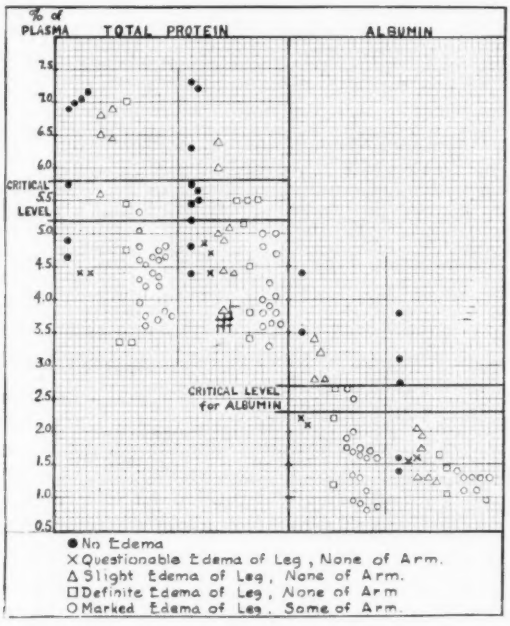

Chart 9.—Concentration of plasma proteins in relation to edema.

and of albumin in the absence of definite signs of edema in our cases, however, was in many instances well below that found by Moore and Van Slyke. These instances all occurred following subsidence of edema.

In our cases, with two exceptions subsequently noted, the concentration above which definite edema was always absent was 2.7 per cent for albumin, and 5.5 per cent for total protein of the plasma, and that below which definite edema was never absent was 1.2 per cent for albumin and 4.4 per cent for total protein. The exceptions to the foregoing rule were one instance in which there was 7 per cent total protein with

definite edema of the leg and none of the arm, and one instance in which there was 3.85 per cent total protein with only slight edema of the leg and none of the arm. The findings of Peters and associates [43b] concerning the lower limit of the concentration of serum proteins compatible with absence of edema are more in keeping with our results than are those of Moore and Van Slyke.[71]

In chart 10, the columns show the protein content of the plasma in the different phases of edema. The total height of the column represents the total protein content and the solid black portion the albumin content. In the instances in which the albumin is indicated in black, the striped portion of the column represents the globulins including fibrin-

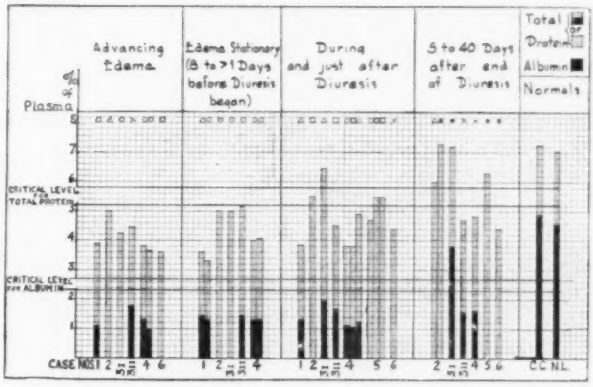

Chart 10.—Relationship of plasma proteins to phase of edema. The symbols above the columns are explained in the key for chart 9. *C.C.* indicates control cases, and *N.L.*, normal cases from the literature.

ogen. The concentration of the protein constituents may be read in percentage of plasma by the scale to the left. The symbol above each column indicates the degree of edema as interpreted in the key for chart 9. The cases are the ones shown in chart 8 and are identified by the numbers below the columns as in that chart. The limits of the concentrations of total protein and albumin above which edema is usually absent and below which edema is usually present in adults, according to Moore and Van Slyke,[71] are indicated by the heavy horizontal lines crossing the chart. It is seen that during the advancing phase and during the stationary phase of edema preceding diuresis, the total protein and the albumin of the plasma were well below the critical level for edema in each instance. During the phase of diuresis and just after diuresis, the albumin fraction is still below the critical level in every instance (six determinations in four attacks of edema), and the total

protein is below the lower limit of the critical level for edema in seven of eleven determinations, in seven attacks of edema. Two of the instances in which the total protein is above the lower limit are in the same case. In other words, diuresis with subsidence of edema occurred when the plasma proteins, especially the albumin, were still in the range in which they are accredited with causing edema. From five to forty days after diuresis, with definite edema absent, the albumin in two of three determinations and the total protein in three of seven determinations are still very low. These data suggest that the increase in albumin and total protein of the plasma follows or accompanies rather than initiates diuresis with loss of edema.

Considering the data more generally, a material change in the relative volume of the cells during the cycle of the edema was accompanied by changes in the same direction of the red blood cell count, of the concentration of total blood solids and of hemoglobin, with some sporadic exceptions in these several elements; and when the relative volume of the cells showed little or no change from the preceding determination there was usually little or no change in these other elements.

The specific gravity of the blood in some cases tended to follow the relative volume of the cells, but in other cases it was little affected by changes in the latter.

The viscosity of the whole blood also tended to increase and decrease with similar changes in the relative volume of the cells. This relationship, however, seemed to be definitely modified in some instances by changes in the concentration of the plasma protein in that an increase or decrease in the protein tended to be accompanied by a corresponding modification in the viscosity.

In evaluating changes in the concentration of the whole blood solids, it must be kept in mind that normally the concentration of solids in the cells is about four times that in the plasma, and that, therefore, a decrease of the relative volume of the plasma will cause an increase in the percentage of the solids in the whole blood, provided that a coincident decrease in the concentration of the solids in the plasma sufficient to counterbalance this does not occur. We found that, like the relative cell volume, the total solids of the blood were in general highest during the development of edema, in some cases higher than normal notwithstanding a dilute plasma, and lowest just before or during diuresis. The concentration of the solids in the plasma, except for three determinations in case 2, was low throughout the course of edema because of the low content of albumin in the plasma. The fibrinogen and other globulins were frequently above normal. The nonprotein solids of the plasma were usually high, in some cases highest during edema and lower during diuresis and later, and in other cases highest after diuresis.

The cholesterol content of the blood, as a rule markedly high during edema, changed little during diuresis and was slow in returning toward normal following diuresis and subsidence of edema.

The time for disappearance of intradermally injected salt solution in the arm and leg corresponded quite well to the degree of edema as determined by pitting on pressure in the same regions. In cases 1 and 3-I, while the weight curve remained level an increase in the disappearance time in the arm occurred several days before the onset of diuresis, thus forecasting an improvement. The change in degree of pitting on pressure also indicated a decrease of edema in the arm at this time. In case 4, also, the disappearance time in the arm was increased on the morning preceding the onset of definite diuresis and loss in weight.

The nonprotein nitrogen content of the blood was above 35 mg. per hundred cubic centimeters in only four instances; 36.3 mg. in one case; 39.2 mg., and 38.4 mg. in another case, and 48 mg. in a questionable determination in a third case. In the last case, however, the nonprotein nitrogen was 30 mg. five days later and remained normal thereafter. In no instance was the nonprotein nitrogen found above normal in a case of nephrosis.

The protein content of the urine (estimated approximately in single specimens) did not as a rule show a definite decrease in the stage just preceding diuresis, as compared with the stage of developing edema.

COMMENT

In a composite case based on the data from the seven cases, the typical findings in the different phases of the edema cycle would be approximately as follows:

I. In the developing phase: a relative volume of plasma of less than normal; a plasma more dilute than normal because of a low concentration of albumin, but with a concentration of fibrinogen and globulin normal or slightly higher than normal, and with nonprotein solids above normal.

II. With edema becoming stationary, preceding onset of diuresis, as compared with the phase of actively developing edema: a greater relative volume of plasma, with the concentration of albumin, globulin and fibrinogen about the same; less edema of the arm, as indicated by less pitting on pressure, and a longer time for disappearance of intradermally injected salt solution.

III. During diuresis, or just at its end, as compared with the stationary phase of edema: a relative volume of plasma further increased and tending to be greater than normal; a concentration of albumin still at about the same low level, and a concentration of globulin somewhat above normal; a rapid subsidence of edema.

IV. In the phase following diuresis: a gradual return of the composition of the blood toward normal.

The first increase of plasma proteins is more evident in the globulin fraction and may occur either in the third or in the fourth phase. The globulin later recedes toward normal as the albumin fraction advances toward normal.

We consider that a substantial decrease of the relative volume of the plasma in our cases indicates a movement of fluids from the blood to the tissues, and, conversely, a substantial increase of the relative volume of the plasma, a movement of fluids from the tissues to the blood. The correctness of this interpretation depends on the presence of a relatively constant absolute volume of blood cells. In our cases, there is no reason to suspect that there was an abnormally rapid production of erythrocytes during the phase of actively developing edema, followed by a rapid loss of erythrocytes shortly before and during diuresis, as would be necessary to produce, by this means, the low relative volume of plasma found in actively developing edema, with the subsequent increase of the relative volume of plasma shortly before and during diuresis. The determinations of the relative volume of plasma in most cases were made at such short intervals during the critical stages in the edema cycle that gradual changes in the absolute volume of cells, such as might result from slowly progressing anemia, would not seem significant in this relation. From these considerations, therefore, we believe that we are justified in assuming that a substantial change in the relative volume of the plasma indicates an actual change in the absolute volume of the plasma and hence in the water content of the blood.

Against the possibility that the changes in the relative volumes of cells and plasma were due to shifting of water between the plasma and the cells, we found that the changes in the cell water (when the data were adequate for this calculation) were sufficient to account for only some of the small changes, and small portions of the larger changes, found in the relative volume of the plasma.

The findings of some of the investigators of the blood and plasma volumes and of the protein concentrations in the plasma during the cycle of edema of the renal type are reviewed in the first portion of this paper. To summarize briefly: Although the studies of Bock [22] and of Brown and Rowntree [23] by a dye method would seem to show no changes in the volume of the plasma attributable to changes in the course of the edema, on the other hand observations on the red blood cell count by Keller [9] and by Nonnenbruch [10] furnish evidence tending to indicate the presence of a low volume of the plasma in the advancing stage of renal edema, as is indicated also by our findings. By methods for the determination of blood and plasma volume, Linder, Lundsgaard, Van Slyke and Stillman,[17] Plesch,[20] Darrow and Buckman,[18] and Waterfield [21] also found

that the volume of the plasma is low during edema and increases with subsidence of edema in certain cases of the renal type.

There is much evidence in the literature that the concentration of protein in the plasma is low in the active stage of renal edema, especially that of the nephrotic type. That it may be low also in some cases during and after subsidence of edema of renal type is shown by the findings of Fahr and Swanson,[31] Moore and Van Slyke,[32] Schwarz and Kohn,[36] Van Slyke and co-workers,[5] Linder, Lundsgaard and Van Slyke [20] and Calvin and Goldberg.[38] Also, Cowie and co-workers [72] reported that in a child with chronic glomerular nephritis in the nephrotic subgroup the serum contained 3.8 per cent total protein and 1.3 per cent albumin during an edema-free period. For the presence of a relative and at times an absolute increase of the globulin and fibrinogen fractions of the plasma protein in this type of edema, there is also considerable support in the literature.

From a consideration of our findings and of the data from the literature, it seems probable that during the actively developing stage of edema of nephrotic type an imbalance exists in the exchange of water between the blood and the tissues that results in a net loss of water by the blood and thus renders water relatively unavailable for excretion by the kidneys. This could be due to: (*a*) a change in the tissues of the body in general that renders water less freely available for resorption by the blood, or (*b*) a change in the blood that decreases its power to resorb water from the tissues, or (*c*) both *a* and *b*. Later, preceding diuresis, the tissues lose some of their excessive water to the blood, and when the water in the blood reaches a sufficiently high level, diuresis begins and is continued by further flow of water from the tissues to the blood, with a consequent disappearance of the edema. The factor that is responsible for the movement of the excessive water from the tissues to the blood could be: (*a*) a change toward normal in the tissues that renders the water more freely available for resorption by the blood, or (*b*) a change toward normal in the blood that increases its power to resorb water from the tissues, or (*c*) both *a* and *b*.

Starling [24] accredited the effect of the proteins on the osmotic pressure of the blood plasma with the function of maintaining a balance in the exchange of fluids between the tissues and the blood under normal conditions. On the basis of Starling's theory, Epstein has attributed edema of the nephrotic type to the low concentration of proteins in the plasma in that condition. The lack of a definite increase, and the occasional occurrence of a decrease, in the concentration of the proteins in

72. Cowie, D. M.; Jarvis, K. M., and Cooperstock, M., with technical assistance of Nakao, A.: Metabolism Studies in Nephrosis with Special Reference to Relationship of Protein Intake to Nitrogen Retention, Edema and Albuminuria, Am. J. Dis. Child. **40**:465 (Sept.) 1930.

the plasma just preceding and during diuresis in the majority of our cases is against the theory that the low concentration of proteins in the plasma is the sole or the chief cause of the edema. Doubtless a low concentration of proteins in the plasma, with the resulting lowered osmotic pressure, favors the development of edema. However, if we are to consider that the low concentration of proteins is the sole cause of edema, we must look for some other factor which determined the onset of diuresis and subsidence of edema in our cases.

Against the probability that the low concentration of the plasma protein is responsible for the low relative volume of the plasma in the advancing stage of edema in our cases is the finding that the relative volume of the plasma usually increased without an increase, and at times even with a decrease, in the concentration of the proteins in the plasma. In this relation, we calculated by means of the factors of Govaerts [42a] the combined, theoretical osmotic pressure of the plasma albumin and globulins in the cases in which the protein fractions were determined, and found no correlation between changes in the protein osmotic pressure and changes in the relative volume of the plasma. At times, with an increase of the latter, the calculated osmotic pressure of the plasma proteins was found to be decreased. Theoretically, within the range of the influence of the concentration of the plasma protein on the formation or the subsidence of edema, an increase in osmotic pressure should precede an increase in the relative volume of the plasma, and, therefore, at the new level of the relative volume of the plasma the osmotic pressure should be found to be greater than, or at least equal to, its value at the previous level of the relative volume of the plasma.

Our observations are in accord with the findings of Kylin [73] and Meyer [74] that the colloidal osmotic pressure of the blood serum frequently remained low and at times even decreased during the disappearance of renal edema.

In evaluating changes in the concentrations of protein and albumin in the plasma from one determination to the next, probably the changes in the relative volume of the plasma should be taken into account, for, by themselves, the changes in the percentages of the plasma proteins do not reflect the changes in the absolute quantities of these proteins. The increases in the percentages of the protein which must be allowed for, in our cases, from a consideration of increases in plasma volumes would seem insignificant as regards a causal relationship of increased albumin in the plasma to initiation of diuresis (the allowance not exceed-

73. Kylin, E.: Studien über die Oedemausschwemmung; IV. Über den kolloidosmotischen Druck des Blutserums während der Oedemausschwemmung, Ztschr. f. d. ges. exper. Med. **68**:746, 1929.

74. Meyer, P.: Untersuchungen über den kolloidosmotischen Druck des Blutes: I. Oedem und Oedemausschwemmung, Ztschr. f. klin. Med. **115**:647, 1931.

ing 0.13 per cent in any instance), and of possible significance in only two cases as regards correlation of the values for total protein with the edema cycle; that is, in case 3-I a further increase of 0.96 per cent of total protein at a point just preceding diuresis, and in case 2 an increase of 0.86 per cent at a similar point in the cycle, must be allowed for.

SUMMARY

The water content of the whole blood and of the blood plasma and the protein content of the plasma were determined at intervals during the cycle of edema of the nephrotic type with the hope of obtaining information of value in disclosing the mechanism of the production of the edema. It was thought that such information might be useful particularly in indicating whether the failure of water elimination is directly attributable to disturbance of renal function, to changes in the tissues of the body in general or to a deficient concentration of proteins in the blood plasma. For example, one might expect to find: (1) a high content of water in the blood during the development of edema becoming normal with diuresis and loss of edema, if the edema is primarily due to a failure of the water-excretory function of the kidneys; (2) a low or normal water content in the blood during the development of edema (unless there should be a concurrent edema of the blood) becoming higher preceding and during diuresis, if the edema is attributable to the holding back of water by the tissues of the body in general, and (3) the same changes as in (2), if the edema is due to a low concentration of proteins in the plasma; in this event, however, a decrease in the plasma proteins should theoretically precede the loss of water in the blood, and an increase in the plasma proteins should precede the increase in the water of the blood and the onset of the evacuation of edema.

Seven cases of nephrosis and glomerular nephritis with the nephrotic syndrome in children were examined at intervals during the cycle of edema especially for changes in the relative volume of the plasma and in the concentration of the solids of the whole blood and of the plasma, and also for changes in the concentration of the proteins in the plasma. It seemed especially important to have determinations as early in the cycle of the edema as possible and again just before and just after the onset of diuresis.

Our findings, in general, were:

1. The relative volume of the plasma was usually low during the development of edema, higher preceding diuresis, still higher and at times above normal during diuresis. It tended to return to normal following diuresis.

2. The concentration of albumin in the plasma was low during the development of edema, with the globulins tending to be normal or slightly higher than normal. During diuresis the plasma proteins remained low with a little increase in some cases, usually most evident in the globulin fraction. After diuresis, in the cases in which the general condition of the patients showed definite improvement, the plasma protein gradually rose toward normal.

3. The concentration of nonprotein solids in the plasma was often greater than normal. This increase could not be accounted for by an increase in the nonprotein nitrogen elements and only partially by an increase in cholesterol content.[75]

We believe that changes in the water content of the blood in our cases are best reflected in the variations in the relative volume of the plasma.

The variations from normal of the relative volume of the plasma during the cycle of edema were just the reverse of what might have been expected if the edema was due entirely to a failure of the water-excretory function of the kidneys.

While the changes in the water content of the blood, considered alone, were, in general, consistent with the theory that low concentration of proteins in the plasma is the cause of edema, yet the fact that the onset of diuresis and loss of edema, in most instances, occurred without significant increase in the concentration of the plasma proteins, especially in that of the albumin fraction, indicates that some other factor, or factors, was important in maintaining the edema and probably, therefore, in producing it.

In the analysis of our data, the amount of increase in the concentration of the proteins in the plasma preceding the onset of diuresis that may have been masked by a coincident increase in the volume of the plasma seems insignificant as regards any influence on the initiation of diuresis, except possibly the increase in the total proteins of the plasma in the two instances previously discussed.

In considering the rôle of a low concentration of plasma protein in the production of edema, possibly one should differentiate between a favoring factor (one causing a tendency or susceptibility to the formation of edema) and an active factor (one determining the actual formation of a clinical edema) and consider the possibility that the withdrawal or abeyance of either of these factors might be sufficient to bring about loss of the edema. The low concentration of the plasma protein in edema

75. Kumpf, by a refractometric method, found the "non-protein constituents" of the serum high in certain cases of renal disease including one of nephrosis. Kumpf, A. E.: The Blood Proteins, with Special Reference to the Changes Occurring in Renal Diseases, Arch. Path. **11**:336 (March) 1931.

of the nephrotic type may be such a favoring factor, and in its presence some additional, active factor may be necessary to bring about a manifest edema. On the other hand, the changes in the water content of the blood during the cycle of the edema are not inconsistent with what might be expected if the edema were due to changes in the tissues of the body in general rendering the water held by them less readily available for resorption by the blood during the development of edema, and freely available for resorption by the blood with improvement preceding and during diuresis.

The conception that the changes which lead to the subsidence of edema are primarily in the tissues gains support from the observation in two of our cases of a lengthening of the time for the disappearance of intradermally injected salt solution in the arm, without an increase in the calculated plasma osmotic pressure due to the proteins, during the stationary phase of edema preceding the onset of diuresis and loss of weight.

CONGESTIVE HEART FAILURE AND ANGINA PECTORIS *

THE THERAPEUTIC EFFECT OF THYROIDECTOMY ON PATIENTS WITHOUT CLINICAL OR PATHOLOGIC EVIDENCE OF THYROID TOXICITY

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Previous studies of the velocity of the blood flow in man [1] have shown that the adequacy of a given velocity of blood flow cannot be decided in absolute terms. It can be evaluated only in relation to the metabolic demands of the particular patient. The best gage of the metabolic needs of the tissues is the basal metabolic rate. Whether or not a patient with heart disease suffers from the signs and symptoms of circulatory insufficiency depends on whether the supply of blood is adequate to the metabolic demands of the tissues. In patients with congestive heart failure and a normal basal metabolic rate, the basal velocity of the blood flow is greatly slowed.[2] The blood flow

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* Further studies in other types of cardiovascular disease are being made, and a more detailed account of precautions, indications and contraindications of the operation will be published in the near future. It is felt that until more experience is available, the operation should be confined to the types of cases described in this communication.

1. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals and a Critique of the Method Used, J. Clin. Investigation **4**:15, 1927; III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Rheumatic and Syphilitic Heart Disease, ibid. **4**:149, 1927; IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, ibid. **4**:173, 1927. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: XIII. The Circulatory Response to Thyrotoxicosis, ibid. **9**:69, 1930; XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia, ibid, **9**:679, 1931.

2. Blumgart, H. L., and Weiss, S.: Clinical Studies on the Velocity of Blood Flow: IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, J. Clin. Investigation **5**:343, 1928; X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, ibid. **5**:379, 1928.

may be similarly slowed in patients with the low metabolic rate of myxedema,[3] but such patients show no clinical symptoms or signs of congestive heart failure. In these patients, therefore, the diminished circulation is evidently adequate to the diminished demands of the body.

The favorable effects of a reduction in the metabolic rate are seen in certain thyrotoxic patients with congestive failure whose circulation becomes compensated after subtotal thyroidectomy. The hearts of such patients are evidently equal to the demands of a normal metabolic rate, though not to the demands of the elevated metabolic rate of thyrotoxicosis. Because of these considerations, the possibility occurred to us that persons with normal metabolism who suffer from congestive heart failure might show striking improvement if the metabolic rate was significantly lowered. The hearts of such persons might be unable to supply enough blood for the ordinary demands of a normal metabolic rate, but might, nevertheless, be able to supply enough blood for the lessened needs of a reduced metabolic rate.

From the clinical standpoint, an observation made by one of us (S. A. L.) [3a] is of interest in the present problem. A patient who was suspected of having masked hyperthyroidism had a subtotal thyroidectomy performed in 1927. Examination of the gland showed a perfectly normal thyroid. In spite of that, however, the patient showed marked clinical improvement. This clinical observation was suggestive that the extirpation of the normal thyroid gland might be helpful in cardiac failure not due to thyrotoxicosis.

This communication presents the clinical results of producing a subnormal metabolic rate by thyroidectomy in three patients who were suffering from severe congestive heart failure but who showed no evidence of disturbed thyroid function and in one patient with angina pectoris with a slight elevation of metabolism but with a normal thyroid gland. The possible advantages of the procedure were offered to these patients because the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. All subjects were completely incapacitated, and the possibility of improvement by all known methods of treatment seemed remote. These patients were chosen because the underlying cardiovascular condition was slowly progressive or relatively stationary; they showed no evidence of syphilitic heart disease; they were not too far advanced in years; and they showed no evidence

3. Blumgart, H. L.; Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow: XIV. The Circulation in Myxedema with a Comparison of Blood Flow in Myxedema and Thyrotoxicosis, J. Clin. Investigation **9**:91, 1930.

3a. Rosenblum, H. H., and Levine, S. A.: What Happens to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? Am. J. M. Sc. **185**:219, 1933.

of active infection. The patients were not gravely ill and the operative risk appeared to be fair. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

REPORT OF CASES

CASE 1.—I. B., a man, aged 45, entered Beth Israel Hospital on Sept. 13, 1932, complaining of shortness of breath of two and a half years' duration. His past history was irrelevant, except for recurrent cholecystitis during the previous twenty years. There was no history of rheumatic infection, diphtheria or venereal disease. During the preceding five years he had had nocturia three or four times. Two and a half years before admission he first noticed shortness of breath and fatigue on walking up hills or on walking up one or two flights of stairs. Soon after the onset of these symptoms, while waiting for a street-car one day, he was suddenly seized with a "tearing, breaking" pain over the entire front of his chest, not related to respiration. The pain lasted ten minutes, and then disappeared as suddenly as it had appeared.

Two years before admission the patient was troubled with dyspnea and palpitation even when he walked on a level surface. On admission to the hospital at that time he had moderate dyspnea and medium moist râles over both lungs from the spines of the scapulae to the bases, but no evidence of fluid in the chest. During the first part of his stay in the hospital he had signs of ascites. The heart was slightly enlarged. The vital capacity of the lungs was 2,000 cc. Electrocardiographic tracings were of the coronary type with a high origin of T_3 and inverted T_1 and T_2. There were left axis deviation and delayed auricular-ventricular conduction, the P R interval being 0.26 second. The blood pressure averaged 176 mm. of mercury systolic and 100 mm. of mercury diastolic. The basal metabolic rate was +3 per cent. On the continuation of a maintenance dosage of digitalis and rest in bed, the patient improved and was discharged. The diagnoses were chronic circulatory insufficiency, hypertensive cardiovascular disease, coronary arteriosclerosis, chronic cholecystitis and cholelithiasis. Operation for the last condition was not advised.

After discharge from the hospital, the patient felt fairly well on a somewhat restricted regimen until eight months before his present admission to the hospital, when he was forced to stay in bed for two months because of cough, dyspnea and weakness. For two months he attempted to supervise his business, but was forced to return to bed or to sit in a chair for the four months preceding his admission to the hospital. During the three weeks preceding entry, the edema of the legs and swelling of the ankles increased, orthopnea became pronounced, and sleep was broken because of dyspnea.

At the time of admission physical examination showed marked dyspnea and orthopnea; there were also deep cyanosis of the lips and mucous membranes, a moderately enlarged heart, no murmurs, sounds of fairly good quality, a gallop rhythm and a regular rate, 100 per minute. The arterial blood pressure was 180 systolic and 110 diastolic. Medium moist râles were heard from the spine of the scapula to the base over both sides except on the left side posteriorly, where signs of a moderate amount of fluid were evident. The abdomen was moderately distended owing to ascites. The tender edge of the liver was felt 3 fingerbreadths below the right costal margin. Moderate pitting edema of the lower part of the legs and of the hands and forearms was present.

Examination of the red and white cells of the blood gave normal results. Chemical analysis of the blood likewise gave normal results except for an icteric index of 25, which became normal after a few days of rest in bed. The electrocardiographic tracings showed normal sinus rhythm and delayed conduction, the P R interval varying from 0.24 to 0.30 second on different occasions.

Xanthine and mercurial diuretics were given repeatedly during the first twelve days, and the patient's weight decreased from 148 to 124 pounds (67.1 to 56.2 Kg.), his state of nutrition remaining approximately the same. In order to estimate the rate of gain of the edema during rest in bed, the patient was given no diuretics between the twelfth and thirty-first days, the rest of his regimen being unchanged. During this period of nineteen days, the gain of edema was progressive. His weight increased 11½ pounds (5.2 Kg.), and edema of the legs reappeared. The vital capacity of the lungs was 1,200 cc. Because of the progressive gain of the edema in spite of all the usual measures, the possible therapeutic effects of thyroidectomy were offered to the patient. After the administration of diuretics, a subtotal thyroidectomy was performed, a minute posterior shell of the gland being left in each tracheo-esophageal sulcus. This operation was performed on Oct. 17, 1932, on the thirty-fifth day of the patient's stay in the hospital.[4] Grossly and microscopically, the gland was normal.

The patient's convalescence was uneventful. One week following the operation, the basal metabolic rate had dropped from +7 to —7 per cent, and the signs of fluid within the chest had cleared up, although medium moist râles were still audible at the bases. The edge of the liver was no longer palpable. There was no edema of the legs or of the sacrum. During the following forty-five days, the basal metabolic rate averaged —14 per cent, and the patient gained 8 pounds (3.6 Kg.). During the nineteen days preceding operation, when the basal metabolic rate averaged 7 per cent, he had gained about 11 pounds (5 Kg.). Part of the postoperative gain in weight was undoubtedly due to the increased intake of food, for he felt much better and ate a full diet. An x-ray picture of the chest showed marked clearing of the pulmonary fields and a decrease of 1 cm. in the transverse diameter of the heart. The lack of gain in edema was striking, for whereas he had craved fluids before operation and had been on a restricted intake of 1,500 cc. of fluid and a salt-poor diet, he was given 6 Gm. of salt in his diet following operation and was permitted to drink all the fluids he wished. In addition, he was permitted to be up and about the ward for most of the day instead of being in bed. This lessened tendency for the edema to progress was reflected by a marked improvement in the patient's symptoms. The vital capacity of the lungs, which had ranged from 1,350 to 1,700 cc. before operation, varied from 1,800 to 2,000 cc. after operation.

The definite improvement in the patient's clinical condition, accompanied by a fall in the basal metabolic rate from +7 to —18 per cent, was not fully maintained after about the fiftieth day following operation. The basal metabolic rate gradually rose approximately to zero, and he gained edema more rapidly than during the fifty days when his metabolic rate was lower. It should be noted that the rate of formation of edema, even during this latter period when he was up and about the ward practically the entire day, was not as great as that observed before operation when he was confined to bed. We felt that the rise in the basal metabolic rate was caused by the fact that the remaining thyroid tissue had undergone hyperplasia. The patient is accordingly being treated by

4. This operation and those performed in the succeeding cases were carried out by Dr. David D. Berlin.

roentgen irradiation, for although there is evidence that roentgen rays are not destructive to normal glandular tissue, it is possible that hyperplastic regenerating tissue may be more sensitive.

Although the patient's condition is not so good as during the period when his metabolic rate was lower, he is nevertheless greatly improved in comparison to his preoperative state. It was felt that it would be of interest to have him describe as clearly as possible his present condition and that before operation. When asked to state in what respects he felt worse and in what respects he felt better, the patient said that before operation he suffered with insatiable "terrible thirst," and was able to sleep fitfully only by the nightly use of sedatives, and that he was unable to walk because of shortness of breath and swelling and stiffness of the legs. Following operation, the craving for water entirely disappeared, and he experienced no difficulty in breathing or walking, though he was up and about the ward almost the entire day.

Case 2.—H. B., a man, 54, unemployed, entered Beth Israel Hospital on Nov. 1, 1932, for the fifth time in two and a half years because of recurrent edema of the legs, pain in the right upper quadrant of the abdomen and shortness of breath. His last discharge from the hospital was six months before the present admission. The diagnoses were arteriosclerotic heart disease, auricular fibrillation, generalized arteriosclerosis and Paget's disease. During the interim the signs and symptoms of congestive failure had continued, and he had been confined to bed practically the entire time.

Physical examination showed cyanosis, orthopnea, a grossly irregular action of the heart and a greatly enlarged heart. The tender edge of the liver was palpable 1 handbreadth below the right costal margin, and there was moderately deep pitting edema over the lower part of the legs, the feet and sacrum. A moderate number of moist râles were heard over both lungs, particularly at the bases. Laboratory examinations of the blood, urine and stool gave no significant findings. The blood pressure was 140 systolic and 70 diastolic. A roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the chest to be 29.4 cm., and the transverse cardiac diameter, 22.1 cm. Electrocardiographic tracings showed auricular fibrillation and bundle branch block; the ventricular rate was 80 per minute. During the first eight days in the hospital, there was no loss of edema with the patient at rest in bed. Two cubic centimeters of mersalyl was then given. Following diuresis from the tenth to the twentieth day, the patient gained 3 pounds (1.4 Kg.) accompanied by a slight increase in the clinical signs of congestive failure. During his entire preoperative period, fluids were limited to 1,500 cc., and the diet contained approximately 4 Gm. of salt. The basal metabolic rate was determined repeatedly and was —4 per cent. Mersalyl was again administered on the twenty-first day. On the twenty-third day (Nov. 29, 1930), subtotal thyroidectomy was performed.

Convalescence was satisfactory. From the eighth postoperative day, when daily weighing was again resumed, to the eighteenth postoperative day, the patient's weight remained stationary, and he had no signs of increasing edema. The gradual loss of his extreme preoperative craving for water was striking. The vital capacity of the lungs averaged 1,500 cc., whereas it had averaged 1,200 cc. before operation; these averages represented the mean of several daily readings. The liver decreased appreciably in size and was definitely less tender, and the patient felt much more comfortable. This clinical improvement was paralleled by a fall in the basal metabolic rate from an average of —4 per cent before operation to —15 per cent.

Following this period, the patient again tended to gain edema, and the clinical course was not so favorable. The basal metabolic rate again rose to the preoperative levels. This change in the basal metabolic rate and in the clinical course was interpreted as being due, in all probability, to regeneration of the thyroid remnants, and roentgen therapy is now being carried out.

Case 3.—G. F., an unemployed cook, aged 52, entered Beth Israel Hospital complaining of shortness of breath, palpitation, constant sense of pressure over the chest and weakness. His past history showed that he had had diphtheria, scarlet fever and rheumatic fever at the age of 12. The attack of rheumatic fever in childhood forced him to remain in bed for three months. He had also had frequent recurrent attacks of sore throat and tonsillitis. He felt quite well until three years prior to the present entry when, while working, he experienced severe pain in the precordial region, which radiated to the left shoulder and down both arms to the tips of the fingers. He was extremely dyspneic. The symptoms were relieved by a hypodermic injection, and after three days in bed he returned to work. After two and a half months, however, he was forced to go to a sanatorium because of increasing dyspnea and weakness. Two and a half years before admission he left the sanatorium, feeling quite well except for a sense of pressure over his chest. He attempted to work, but, because of dyspnea and weakness he was again forced to go to bed. The foregoing symptoms gradually became more and more severe, although he refrained from work and rested most of the day. During the last two years, he had noticed a gradual increase of edema in the legs.

He entered this hospital in the ward service eight months before the present admission, and at that time the findings on physical examination were essentially as at present. A note by a visiting physician at that time stated that the prognosis was not good and that the patient would be a cardiac invalid for life. The patient's condition improved on rest in bed, so that on discharge three weeks later he had only a slightly enlarged liver and minimal pitting edema of the legs. On discharge the diagnoses were arteriosclerotic heart disease, auricular fibrillation, (?) rheumatic heart disease and emphysema of the lungs.

Because of the continued evidence of the signs and symptoms of congestive heart failure, he was discharged to the state hospital for chronic diseases, where he was allowed table and lavatory privileges. He had a recurrence of his orthopnea, edema of the legs, enlargement of the liver, attacks of precordial pain and constant sense of pressure over the chest. Later he went to the Bickur Cholim Hospital for chronic diseases, where his condition remained essentially unchanged. He was seen by us at the Bickur Cholim Hospital, and because of his prolonged invalidism, in spite of all known medical procedures, the possibility of a total thyroidectomy was offered.

On the patient's entry to Beth Israel Hospital physical examination showed orthopnea, slight cyanosis of the lips and mucous membranes and marked enlargement of the heart, the apex impulse being seen and felt in the sixth interspace in the anterior axillary line. The heart sounds were grossly irregular but of fairly good quality. There was a soft blowing systolic murmur which partly replaced the first sound and which was best heard over the mitral area and transmitted toward the left axilla and the base of the heart. The pulmonic second sound was greater than the aortic second sound. A faint middiastolic murmur was heard just below and to the left of the nipple. No aortic diastolic murmur was heard. The tender edge of the liver was palpable 3 fingerbreadths below the right costal margin. There was definite pitting edema over the legs and the sacrum. The blood pressure was approximately 125 systolic and 60 diastolic.

There were scattered moist râles over both lungs, particularly at the bases. The apex and radial pulse rates were 64 per minute. A roentgenogram taken at a distance of 7 feet showed the total transverse diameter of the heart to be 17.4 cm.; the transverse diameter of the chest was 29.5 cm. Electrocardiographic tracings showed auricular fibrillation, QRS waves of rather small amplitude and diphasic T_1 and T_2. The vital capacity of the lungs was 2,000 cc. The basal metabolic rate was —1 per cent. Routine examinations of the blood and urine gave normal results. The diagnoses were auricular fibrillation, congestive heart failure, mitral stenosis and regurgitation and (?) probably old healed coronary thrombosis.

During the patient's preoperative stay in the hospital of twenty-one days, the vital capacity of the lungs varied from 2,000 to 2,700 cc. The evidences of congestive failure decreased, although they did not disappear entirely, and the weight decreased 3¾ pounds (1.7 Kg.) following diureses caused by repeated injections of mersalyl. Because there was evidence of regeneration after subtotal thyroidectomy in the preceding two patients, a complete total thyroidectomy was performed on this patient on Dec. 15, 1932, the parathyroid glands being spared. The patient had an uneventful convalescence. Eight days after operation the basal metabolic rate was —7 per cent; two weeks after operation, —14 per cent, and three weeks after operation, —16 per cent. During the four weeks from then until the time of writing, Feb. 1, 1933, the basal metabolic rate has been approximately —28 per cent. For the last four weeks he has been up and about the ward for increasing periods of time, until at the present writing he is up practically the entire day and helps about the ward in performing minor duties, such as serving trays.

The change in the patient's clinical condition has been conspicuous. Instead of being orthopneic, he now sleeps flat in bed, and his craving for water has entirely disappeared. Instead of gaining edema, as occurred previously when he got out of bed even for part of the day, he is now underaking moderate exercise without showing any signs or symptoms of congestive heart failure. Whereas before operation even combing his hair or turning over in bed caused violent palpitation, he now states that for the first time in three years he is "unaware that he has a heart." The sense of thoracic compression with numbness and occasional pain in the left arm from which he has suffered continuously for three years has not been present for over four weeks. He no longer complains of perspiration, and during the last two weeks he has spontaneously asked to be discharged from the hospital in order that he may return to work. It is interesting to note that in spite of his lowered metabolism and a somewhat increased sensitivity to cold, he states that his mental processes are more acute than formerly. This we interpret as being due to the fact that he compares his present state with his state of grogginess during congestive heart failure. He states that he thinks as keenly as he did about three or four years ago. The vital capacity of the lungs is now 3,100 cc. This increase is significant and may be considered to be the result of lessened congestion of the lungs.[5] The transverse diameter of the heart is essentially the same as previously. There has been no significant change in the velocity of the blood flow.

5. Means, J. H.: Dyspnoea, Medicine **3**:309, 1924. Drinker, C. K.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, J. Exper. Med. **35**:77, 1922. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: V. The Physiological and the Pathological Significance of the Velocity of Blood Flow, J. Clin. Investigation **4**:199, 1927.

CASE 4.—J. L., a factory foreman, aged 51, complained of a squeezing pain in his chest and arms. His illness began in 1928. He first noticed that if he walked hurriedly this pressure pain would develop in his chest and extend down both arms and would last about five minutes. In addition, he had a different kind of discomfort which he called heart burn, which he had had for many years. It came on about two hours after meals and was relieved by sodium bicarbonate.

He was first seen as an ambulatory patient on May 26, 1931, and showed nothing striking on physical examination. The blood pressure was 148 systolic and 82 diastolic. The heart was not enlarged, and there were no murmurs. The rhythm was regular with an occasional premature beat. The first heart sound was slightly diminished in intensity. Examination of the lungs and abdomen gave negative results. The urine was normal. The vital capacity of the lungs was 4,000 cc. An electrocardiogram showed left ventricular preponderance and flat T waves in lead I.

The patient was regarded as having definite angina pectoris and probable duodenal ulcer. Glyceryl trinitrate gave him prompt relief from the attacks of pain in the chest. He was also told to take five small meals a day instead of his customary three meals.

When he was next seen on May 20, 1932, it was learned that his condition had remained the same until two months previously, when the attacks of angina became more severe. The results of physical examination were unchanged. Because his skin was somewhat moist, although there was no exophthalmos, thyroid enlargement or tremor, he was given 10 drops of compound solution of iodine once a day and 0.1 Gm. of euphyllin (theophyllin ethylenediamine) three times a day. He was again seen on October 18. He had had practically no attacks all summer, but during the preceding month he had had to use one or two pills of glyceryl trinitrate a day because of recurrent attacks. The attacks also began to occur while he was at rest without making any effort.

He entered Beth Israel Hospital on October 23. The basal metabolic rate was +25 and +30 per cent. He had been taking iodine during the previous five months. It was decided that a subtotal thyroidectomy should be performed, although the only evidence of hyperthyroidism was the moist skin and slightly elevated metabolism. It was felt that whether the gland was pathologic or normal some good might result from the operation. Treatment with 10 drops of compound solution of iodine three times a day was therefore continued. The metabolic rate was + 10 and 12 per cent on October 30, and on November 1, a subtotal thyroidectomy was performed, about one tenth of the gland in the tracheo-esophageal sulcus being left. On November 19, the basal metabolic rate was —5 per cent. The thyroid gland appeared normal to the surgeon, and the report of the pathologist was that the thyroid gland was normal grossly and microscopically.

The patient left the hospital on November 19; he returned to work, and has had no attacks of angina since the operation. The first improvement during the previous summer may have been due to the warm weather. It may also have been due to the iodine or to the euphyllin. The final disappearance of the angina during the winter could not have been due to any of these causes, and seemed to be the specific result of the thyroidectomy. He now not only has no anginal pain while at rest or during excitement, but has been able to walk distances without distress, which he had found impossible before operation.

COMMENT

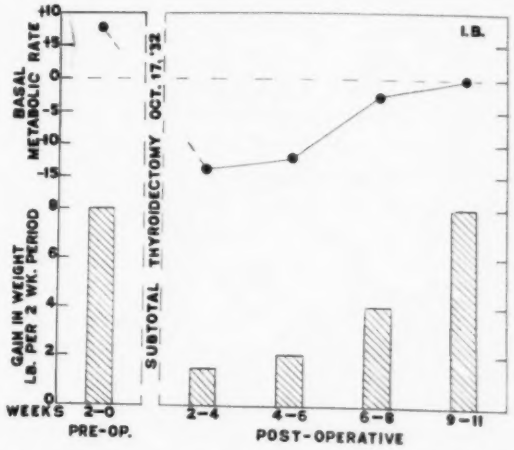
In evaluating the effects of any therapeutic procedure, one must guard against the possibility of suggestion or of spontaneous changes in the clinical course of the disease as accounting for the patient's improvement in symptoms. For this reason, patients have been selected for study whose clinical course has remained practically unchanged over a long time, and who have received medical evaluation of their condition from time to time before coming to the hospital.

In cases 1 and 2, subtotal thyroidectomy caused a fall in the metabolic rate, which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowering of metaobilsm and was evidenced by the absence of edema, the increased vital capacity of the lungs and the ability to be up and about the ward without discomfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level, and the clinical conditions became less favorable. The patient in case 1 continued for an additional month to show a metabolic rate somewhat lower than before operation, and his clinical condition, while not as good as that three weeks following operation, was definitely better than before operation. Before operation, accurately controlled observations over a period of five weeks showed that even while he rested in bed he gained edema spontaneously at the rate of about 5 pounds (2.3 Kg.) a week. During the latter part of the study he was up and about the ward for most of the day and was no longer orthopneic, and in spite of his markedly increased activity he did not have as rapid a gain of edema as before operation (chart). This is in pronounced contrast to his clinical state before operation, when he was forced to remain in bed at home continuously for more than eight months.

Because the metabolic rate of these two patients did not remain persistently lowered, it was decided to perform total thyroidectomy on the third patient. The parathyroid glands were identified, and total ablation of all thyroid tissue was done. The patient had an uneventful convalescence, and about six weeks after operation had a basal metabolic rate ranging from —25 to —30 per cent. At the time of writing, he is up and about the ward practically the entire day, feels strong, is no longer orthopneic, has absolutely no signs of congestive heart failure and is eager to leave and return to work. The fact that this patient showed no such change while in hospitals for the care of patients with chronic diseases during the last two and a half years and no improvement after all the usual medical measures had been invoked under our observation makes us confident that the striking change in his clinical condition can safely be attributed to the sustained lowering of the basal metabolic rate effected by total ablation of the thyroid.

The patient states that whereas previously even combing his hair or turning over in bed was attended by severe palpitation, he no longer suffers from such distress. For the first time in years he is able to sleep lying flat in bed. The sense of substernal oppression from which he had suffered for three years has disappeared.

The fourth case deserves special comment. The patient had been suffering from typical angina pectoris for four years. He lacked all the classic evidences of hyperthyroidism, such as exophthalmos, palpitation, enlargement of the thyroid gland, tremor, nervousness, loss of weight or increase in the velocity of the blood flow. The basal metabolic rate, however, was slightly elevated, being about 25 per cent,



Relation between the lowered basal metabolic rate and the rate at which edema formed in the patient in case 1 while he was at rest in bed.

and the skin was moist. He might have been regarded as having a case of masked hyperthyroidism,[6] but when the thyroid gland was removed it was found to be normal. The metabolism was definitely lowered by the operation, and with this the anginal attacks disappeared.

Studies of the velocity of the blood flow in these patients show that in spite of clinical improvement the speed of the blood flow remains the same as that previous to operation. It appears, therefore, that we

6. Levine, S. A., and Sturgis, C. C.: Hyperthyroidism Masked as Heart Disease, Boston M. & S. J. **190**:233, 1924. Levine, S. A., and Walker, G. L.: Further Observations on Latent Hyperthyroidism Masked as Heart Disease: Angina Pectoris, New England J. Med. **201**:1021, 1929. Levine, S. A.: Unrecognized Hyperthyroidism Masked as Heart Disease, Ann. Int. Med. **4**:67, 1930.

have not altered the fundamental state of the circulation. In terms of the law of supply and demand, we may say that the supply of the blood has not been increased, but the demands have been reduced to such an extent that the reduced supply is now adequate to the ordinary needs of daily life under these new circumstances. The latter considerations add further confirmation to the fact that the improvement may be attributed to the effects of thyroidectomy. In an extensive series of patients with cardiac disease whose velocity of blood flow was studied, it was found that when clinical improvement occurs under the usual medical procedures, the metabolic rate presumably remaining unchanged, the clinical improvement is attended by an increased speed of blood flow.[7] Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation more accurately. Until this is accomplished, the operation is indicated in only a relatively small group of patients who have been observed over a considerable period of time, for, as is well known, the natural course of cardiovascular disease is often irregular. Advanced arteriosclerosis, impaired renal function, syphilitic cardiovascular disease, active rheumatic infection or active phases of acute coronary thrombosis are adverse factors. Similarly, if the course of the disease seems rapidly progressive, operation is obviously contraindicated. In performing thyroidectomy, injury to the parathyroid glands must be avoided. The special surgical details which must be observed will be given in a forthcoming communication. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove to be beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

SUMMARY

Reasons are given for believing that patients with a normal metabolism who suffer from congestive heart failure or angina pectoris might show striking improvement if the metabolic rate were significantly lowered. The hearts of such people might be unable to supply enough blood for the ordinary demands of a normal metabolic rate, but nevertheless might be able to supply enough blood for a reduced metabolic rate. The present communication reports the results of producing a subnormal metabolic rate by thyroidectomy on three patients who were suffering from severe congestive heart failure but who showed no

7. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, Medicine **10**:1, 1931.

evidences of disturbed thyroid function, and on one patient with angina pectoris with a slight elevation of metabolism but with a normal gland. In the patients studied the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

In two of the three patients with severe congestive heart failure subtotal thyroidectomy caused a fall in the metabolic rate which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowered metabolism and was evidenced by the disappearance of edema, the increased vital capacity of the lungs and the ability to be up and about the ward without discomfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level, and their clinical conditions became less favorable. One of these patients continued for an additional month to show a somewhat lessened metabolic rate than before operation, and his clinical condition, while not so good as that three weeks following operation, was definitely better than before operation. The patient with angina pectoris has shown no recurrence of the attacks of angina pectoris since subtotal thyroidectomy, although he has returned to work and active life. This is in contrast to his condition before operation, when attacks of angina pectoris occurred even while he was at rest.

In one patient with congestive heart failure complete ablation of all thyroid tissue was done, the parathyroid glands being spared. This patient has maintained his conspicuous clinical improvement and the metabolic rate has remained persistently lowered for more than six weeks. Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation more accurately. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

NATURE OF SKIN REACTIONS PRODUCED BY HEAT-INACTIVATED POLIOMYELITIS VIRUS

REACTION OF PERSONS CONVALESCING FROM POLIOMYELITIS AND OF NORMAL PERSONS TO INTRACUTANEOUS INJECTIONS OF THE HEAT-INACTIVATED VIRUS

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The purpose of the present investigation was to determine whether or not persons who had recovered from poliomyelitis or those who are generally considered resistant to it possess any cutaneous allergy to the heat-inactivated virus of the disease. Our aim, obviously, was to devise a skin test which would differentiate between susceptibility and resistance to poliomyelitis on a specific immunologic basis. Although there are no known manifestations of the human disease which suggest the operation of an allergic mechanism, the extensive study of experimental poliomyelitis in monkeys has brought forth various observations for which hypersensitiveness or allergy to the virus has been considered as one of the possible explanations by certain investigators.[1] Recently, one of us (C. W. J.[2]) showed that monkeys that have recovered from experimental poliomyelitis respond with an accelerated rise of temperature to an intracranial or subcutaneous injection of the virus, and interpreted this phenomenon as a specific, allergic, febrile reaction. The possible practical application of this observation

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1. Roemer, P. H.: Epidemic Infantile Paralysis, English translation, New York, William Wood & Company, 1913. Shaughnessy, H. J.; Harmon, P. H., and Gordon, F. B.: The Resistance to Poliomyelitis of Animals Previously Inoculated with Heated Virus, J. Prev. Med. **4**:157, 1930. Brebner, W. B.: Evidence of Possible Occurrence of Anaphylactic Phenomena in Poliomyelitis Immune Monkeys, Proc. Soc. Exper. Biol. & Med. **29**:351, 1932.

2. Jungeblut, C. W.: An Accelerated Febrile Reaction in Monkeys Upon Reinoculation with Poliomyelitis Virus, J. Exper. Med. **53**:159, 1931.

led to an investigation of the reaction of persons convalescing from poliomyelitis to the injection of heat-inactivated poliomyelitis virus. Preliminary tests [3] on twenty-seven children and youths with residual paralysis showed that all of them responded with a delayed skin reaction (maximum development in twenty-four hours) at the site of the intracutaneous injection of heat-inactivated virus..

The recent epidemic of poliomyelitis in New York City and vicinity stimulated a more extensive and critical study of this problem. The plan involved the testing of a certain number of persons convalescing from poliomyelitis and normal adults who generally are known to have a high resistance to the disease, and comparison of their skin reactions with those obtained in normal children of the susceptible age groups. The investigation as originally planned also included a study of similar tests on patients in various stages of acute poliomyelitis.

NATURE OF PREPARATIONS USED FOR INTRACUTANEOUS TESTS

The virus-containing solutions were prepared from the spinal cords of monkeys with typical experimental poliomyelitis; for control, similar extracts were prepared from the spinal cords of normal monkeys. The cords, which were preserved in glycerin for varying periods of time after their removal, were ground up with sand and physiologic solution of sodium chloride, and 5 per cent suspensions were prepared in the usual manner. After centrifugation, the supernatant liquid was heated at 65 C. for one hour, which is more than sufficient to inactivate the virus completely. During the heating a flocculent precipitate appeared in most preparations; after filtration through a Seitz or a Berkefeld N filter, the solutions were tested for sterility by culture and for the absence of active virus by intracranial injection into monkeys. Except when otherwise indicated, the solutions were not used until two or more months after their preparation. In tests 1, 2 and 7, the Aycock-1916 strain of virus was used; in the other tests, the mixed Rockefeller Institute virus and our own 1931 human virus were used in addition to the Aycock strain.

DESCRIPTION OF THE INTRACUTANEOUS TESTS

Two-tenths cubic centimeter of the various solutions was injected intracutaneously into the flexor surface of the forearms. The site of inoculation was usually observed for about half an hour after injection, and then after from six to eight hours, and again after twenty-four hours. In a few sensitive persons an immediate urticarial reaction

3. Jungeblut, C. W.: Allergic Reactions in Polio-Convalescent Children After Intracutaneous Injection of Heat-Inactivated Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **28**:1072, 1931.

occurred with both the virus cord and the normal cord preparations; these reactions disappeared completely within from two to three hours. Positive, delayed reactions consisted of edema and erythema of varying degree. The extent of the reactions was measured in millimeters; those that were less than 10 by 10 mm. were not considered positive for the purpose of this paper. While this practice eliminated a certain number of weak reactions, an arbitrary line in recording the results had to be drawn somewhere for purely practical reasons

TABLE 1.—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Children and Youths* *

Name	Age, Years	Interval Since Onset of Paralysis, Years	Monkey, Polio Cord		Monkey, Normal Cord	
			24 Hours	36 Hours	24 Hours	36 Hours
K. I.	6	5	0	0	0	0
T. C.†	16	15	0	+	0	0
V. D. R.†	16	2	++	+	0	0
M. N.†	23	16	++	+++	0	0
P. C.†	15	14	+	0	0	0
F. C.‡	16	4	0	0	0	0
E. R.	2	1	0	0	0	0
D. B.‡	15	14	0	0	0	0
T. G.	4	?	0	0	0	0
E. E.	10	8	0	0	0	0
M. H.	13	8	+	0	0	0
H. P.	2	?	0	0	0	0
A. C.	2	1	0	0	0	0
E. D.	16	No history of poliomyelitis	0	0	0	0
O. W.	11		0	0	0	0
O. B.	10		0	0	0	0
A. G.	13		+	++	0	0
L. M.	10		0	+	0	0
A. B.	15		0	0	0	0
L. P.	10		+	0	0	0
B. H.	10		0	0	0	0
O. R.	14		0	0	0	0
R. B.	15		0	0	0	0
E. L. R.	8		++	++	0	0
F. T.	9		++	++	0	0

* No reaction or slight redness up to 9 × 9 mm. = 0. Redness 10 × 10 mm. to 19 × 19 mm. = +. Redness 20 × 20 mm. to 29 × 29 mm. = ++. Redness 30 × 30 mm. to 39 × 39 mm. = +++.
† Serum failed to neutralize virus in vitro.
‡ Serum neutralized virus in vitro.

1. *Skin Reactions of Children and Youths Convalescing from Poliomyelitis and of Normal Subjects.*—In this test, thirteen children and youths convalescing from poliomyelitis, with residual paralysis for periods varying from one to sixteen years, and twelve who had no history of poliomyelitis were given injections of a heat-inactivated preparation of monkey virus and a similar preparation of normal monkey cord (table 1). Whereas none reacted to the normal monkey cord, four from each group exhibited positive skin reactions with the virus. However, the incidence of clearcut positive reactions was so low, when compared with the uniformly positive results observed in the preliminary test, that it appeared to be due to a diminished concentration of the reaction-producing principle. Whether or not this variation depended on a decreased concentration of virus was neither clear nor definite.

2. Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults and Young Children.—The purpose of this test was to observe the effect of other preparations of virus and normal monkey cords, and to compare the reactions of persons convalescing from poliomyelitis with those of normal adults and young children (table 2).

TABLE 2.—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults and Young Children* *

Group	Name	Age, Years	Monkey, Polio Cord		Monkey, Normal Cord	
			7 Hours	24 Hours	7 Hours	24 Hours
Persons convalescing from poliomyelitis	L. V.†	7	+	0	+	0
	Gr.†	19	+	+	0	0
	P. C.‡	19	+	0	+	0
	Kl.	16	0	+	0	0
	Cr.†	15	0	+	+	0
	Ri.‡	18	+	+	+	0
	Po.	18	+	++	0	0
	Ru.	13	0	0	0	0
	De.	9	+	+	0	0
	Ge.	9	+	+	+	+
	D. B.‡	15	+	0	+	0
	M. H.	13	+	+	+	+
	F. M.‡	12	+	+	0	0
	M. S.	13	0	0	0	0
	L. R.	?	++	++	0	+
	P. C.†	15	0	0	0	0
	B. L.	?	0	+	0	0
	F. C.‡	16	0	0	0	0
	A. B.	19	0	+	0	0
	E. E.	10	0	0	0	0
No history of poliomyelitis	Co.	From 20-45 years of age	+	0	+	0
	Ju.†		+	+	++	+
	Fr.‡		+	+	+	+
	HA.		++	++	++	+++
	Cl.		++	++	++	++
	Ho.		++	+	++	+
	St.		+	0	+	0
	In.		0	0	0	0
	Sa.		+	0	+	++
	En.		++	0	++	+
	Bu.†		+	0	+	0
	To.		+	+	+	+
	Jo.		+	0	+	0
	St.		0	++	0	++
	Se.		0	0	0	0
	Ka.		0	++	0	0
	Ga.		++	+	++	+
No history of poliomyelitis	A. S.	3 weeks	..	All negative	..	All negative
	J. M.	1 month				
	R. W.	1 month				
	J. S.	1 month				
	N. A.	1 month				
	L. Y.	6 months				
	M. N.	1 year				
	E. L.	1 year				
	W. D.	2½ years				
	M. D.	2½ years				
	E. A.	2¾ years				
	B. L.	2¾ years				
	F. S.	3 years				
	E. B.	3½ years				
	P. B.	5 years				
	M. S.	6 years				
	C. N.	6½ years				
	N. S.	7 years				
	D. W.	8 years				
	C. L.	8 years				
	R. O.	9½ years				
	F. D.	10 years				

* No reaction or slight redness to 9 × 9 mm. = 0. Redness 10 × 10 mm. to 19 × 19 mm. = +. Redness 20 × 20 mm. to 29 × 29 mm. = ++. Redness 30 × 30 mm. to 39 × 39 mm. = +++. Redness 40 × 40 mm. to 49 × 99 mm. = ++++.

† Serum failed to neutralize virus in vitro.

‡ Serum neutralized virus in vitro.

In a group of twenty convalescents (varying in age from 7 to 19 years), after the injection of the virus solution there were ten slightly positive reactions and two more strongly positive ones at the end of twenty-four hours; in the same group, only three persons showed slightly positive reactions to the preparation of normal monkey cord twenty-four hours after injection, while seven had reacted to the control material at the earlier reading. In the group of seventeen normal adults, the ages varying from 20 to 45 years, there were five slightly positive and four strongly positive reactions to the virus-containing solution at the end of twenty-four hours, but practically just as many and as severe reactions to the control solution prepared from normal monkey cord. The latter positive reactions, which were indistinguishable from those obtained with the virus solution, naturally raised the question whether there is any specific difference between the reaction-producing principles in the two solutions. It appeared rather as though the reactions were complicated by some peculiarity in the skin of different persons, there being a tendency with increasing age to react more markedly to either of the two products. Thus it will be seen that none of the group of twenty-two normal children (varying in age from 3 weeks to 10 years) who were given injections of the same material showed any positive reactions at the end of twenty-four hours to either the virus or the control solution. However, even if one should be inclined to regard the positive skin reactions of the persons convalescing from poliomyelitis and of some normal adults as specific allergic reactions to the virus, the failure to obtain such reactions in all of the young children is not in good agreement with the expected number of susceptible subjects among them.

3. *Skin Reactions of Normal Adults and of Adults Convalescing from Poliomyelitis to the Mixed Rockefeller Institute Monkey Virus and the 1931 Virus Derived from Human Spinal Cords.*—Since certain preparations of normal monkey cords gave skin reactions that were indistinguishable from those produced by the virus solutions, the proper interpretation of the test became very confusing. Moreover, the irregularity with which virus solutions elicited these skin reactions in persons convalescing from poliomyelitis called for more extensive tests with various poliomyelitis monkey cord preparations.

The mixed Rockefeller Institute virus, which had undergone numerous monkey passages in the Research Laboratories of the New York City Department of Health, was used in this test. The preparation was passed through a Seitz filter, and before heating as little as 0.05 cc. produced typical poliomyelitis in a monkey. Since in most of the other preparations a flocculent precipitate formed during the heating, there was no certainty as to how much of the virus actually remained in the

clear solution; in the present preparation, however, no flocculent precipitate formed, so that one could feel assured of a definite content of heat-inactivated virus. A new extract of normal monkey cord was prepared in the same manner. Largely to eliminate the factor of "foreign protein" and to use the virus before it had been adapted to monkeys, extracts were prepared from suitable pieces of the spinal cords from three patients who died of poliomyelitis in 1931; before heating, the emulsion produced typical poliomyelitis in monkeys. This test differs from previous tests also in the fact that all of the solutions were used three days after their preparation.

Fourteen normal adults, four persons convalescing from poliomyelitis with residual paralysis and three who gave histories of so-called

TABLE 3.—*Skin Reactions of Normal Adults and of Adults Convalescing from Poliomyelitis to the Mixed Rockefeller Institute Monkey Virus and the 1931 Virus Derived from Human Spinal Cords*

Name	Age, Years	History of Poliomyelitis	Monkey, Normal Cord	Monkey, Pollo Cord; Mixed Virus	Human, Pollo Cord; 1931 Virus
A. L.	21	None	All negative	All negative	All negative
H. F.	22				
A. S.	26				
S. G. F.	24				
H. N.	20				
N. S.	24				
A. G.	20				
E. K.	23				
C. S.	22				
W. B.	32				
A. C.	22				
W.	28				
J. W.	20				
B. S.	30				
C. N. P.	30	"Abortive" poliomyelitis? in 1916	Negative	Negative	Negative
L. A. L.	20				
W. H.	28				
J. J. D.	21	Paralysis 1909	Negative	Negative	Negative
F. A.	24	Paralysis 1916			
C. J.	30	Paralysis 1906			
J. H.	18	Paralysis 1916			

"abortive" poliomyelitis in 1916 were tested with these solutions (table 3). In view of the nature of the preparations, it was most interesting to observe that at from eighteen to twenty-four hours there was not a single positive skin reaction. While a different strain of virus was used in this test and the number of authentic subjects convalescing from poliomyelitis was small, the absence of any reactions with preparations known to contain definite quantities of heat-inactivated virus is difficult to reconcile with the existence of a widespread cutaneous allergy to the heat-inactivated virus of poliomyelitis.

4. *Skin Reactions of Young Children with Poliomyelitis Early After the Onset of Paralysis.*—The purpose of this test was to determine whether or not soon after the onset of paralysis young children

would react differently from older convalescent and normal persons. This test was conducted simultaneously with test 3, and the same solutions were used; in addition to these, an older preparation (about 5 months old), which was used in test 2, was included for comparison. Twelve children, varying in age from 9 months to 10 years, were given injections. They all had definite paralytic involvement, the interval since the onset of paralysis varying from four to eighteen days. With the exception of one child who had received antipoliomyelitic horse serum, none had had any serum therapy. As is indicated in table 4, there was not a single positive reaction in from eighteen to twenty-four hours. The results of this test, however, while in perfect agreement

TABLE 4.—*Skin Reactions of Young Children Suffering from Poliomyelitis Early After the Onset of Paralysis*

Name	Age	Serum Therapy	Days Since Onset of: Symptoms	Days Since Onset of: Paralysis	Human Polio Cord; 1931 Virus	Monkey Polio Cord; 1916 Virus	Monkey Polio Cord; Mixed Virus	Monkey Normal Cord; No Virus
J. P.	9 mos.	None	17	14				
M. Y.	18 mos.	Antipoliomyelitic horse serum	16	14				
A. C.	22 mos.	None	12	11				
T. H.	2½ yrs.	None	9	8				
G. A.	3 yrs.	None	?	11	All negative	All negative	All negative	All negative
E. M.	4 yrs.	None	7	6				
P. L. S.	4 yrs.	None	?	12				
J. M.	4 yrs.	None	13	13				
S. R.	5 yrs.	None	?	11				
G. G.	6½ yrs.	None	15	12				
C. M.	8 yrs.	None	4	4				
J. H.	10 yrs.	None	?	18				

with those of test 4, should not be interpreted without some reservation, since allergy may conceivably not have developed so early in the course of the disease.

5. *Skin Reactions of Older Persons Convalescing from Poliomyelitis to Human and Monkey Strains of Virus.*—This test was conducted in order to observe the reactions of a larger group of older persons convalescing from poliomyelitis to the solutions employed in tests 3 and 4 after they had been kept in the icebox for two months. Five normal adults, two of whom had reacted negatively before in test 3, were given injections of the preparations the day before they were used on the persons convalescing from poliomyelitis; it is interesting to note that one of the solutions (mixed virus cord) induced some doubtful and some slightly positive reactions, practically all of which, however, disappeared within twenty-four hours. Among the twenty-three subjects convalescing from poliomyelitis, there were at the end of twenty-four hours from five to seven positive reactions of varying intensity with either of the two monkey virus preparations as contrasted with a single

positive reaction with the human virus cord. Moreover, three delayed reactions were noted with the normal cord solution in the latter group. The impression was gained that in this test all the preparations, though to a lesser extent than the normal cord, contained some reaction-inciting principle to which the skins of only some persons responded.

6. *Skin Reactions of Persons Convalescing from Poliomyelitis and of Adults to Preparations from Monkey Spinal Cords Preserved by Various Methods.*—The results obtained in the preceding tests sug-

TABLE 5.—*Skin Reactions of Older Persons Convalescing from Poliomyelitis to Human and Monkey Strains of Virus* *

Name	Age, Years	Interval Since Onset of Paralysis, Years	Monkey, Normal Cord; No Virus		Monkey, Polio Cord; Mixed Virus		Monkey, Polio Cord; 1916 Virus		Human, Polio Cord; 1931 Virus	
			6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.
Cr.†	15	14	0	0	±	0	±	0	0	0
K.	9	7	0	0	−	0	±	0	0	0
S.	..	..	0	0	±	0	±	0	0	0
C.†	16	15	0	0	±	−	±	0	0	0
Cu.	12	..	0	0	0	0	0	0	0	0
A.	11	..	0	0	0	0	0	0	0	0
Co.	9	6	0	0	0	±	0	+	0	0
D.	4	..	0	0	0	−	0	0	0	0
A.	..	..	0	0	±	0	±	0	0	−
Bl.	5	..	0	±	0	±	0	±	0	0
Sa.	3	..	0	±	0	0	0	0	0	0
H.	13	6	0	0	+	0	+	±	0	0
G.	9	7	0	−	0	0	0	0	0	0
Ga.	7	6?	0	0	0	++	0	+	0	0
Th.	..	..	0	0	0	0	0	0	0	0
Crt.‡	16	4	0	0	0	0	0	±	0	0
Ba.	19	18	0	0	0	0	0	0	0	0
Ko.	16	14	0	0	0	0	0	0	0	0
Fl.†	13	3	0	0	0	0	0	0	0	0
Et.	10	9	−	0	0	0	0	±	0	0
Ge.	9	2	0	0	0	0	0	±	+	0
Pa.	..	..	0	0	0	0	0	0	0	0
Kl.	17	10;16	0	0	0	0	0	0	0	0
Go.§	10	No	±	0	−	++	+	+	0	0
D. B.	27	history	0	0	−	−	..	..	0	0
A. L.	21	of	0	0	±	0	..	..	0	0
B. G.	18	polio-	0	0	±	0	..	..	0	0
B. B.	27	myelitis	0	0	−	0	..	..	0	0
B. S.	30		0	0	+	0	..	..	0	0

* No reaction or very slight redness to 9 × 9 mm. = 0. 10 × 10 mm. to 19 × 19 mm. = ±. Very faint or faint redness.
10 × 10 mm. to 19 × 19 mm. = +. Definite edema and erythema.
20 × 20 mm. to 29 × 29 mm. = ++. Definite edema and erythema.
† Serum failed to neutralize virus in vitro.
‡ Serum neutralized virus in vitro.
§ Clinically not poliomyelitis; congenital spastic paraplegia.

gested a possibility that the positive reactions produced by some of the preparations might have been due to autolytic or other cord decomposition products which they contained. Thus it seemed advisable to compare the effect of solutions prepared in the routine manner, i. e., from spinal cords preserved in glycerin, with that of solutions prepared from freshly removed, unpreserved cords.

Two spinal cords were obtained from monkeys with typical poliomyelitis; without any preliminary contact with glycerin, one cord was

processed immediately, the preparation being known as "fresh polio cord"; the other was dried in a desiccator to constant weight and then used for the preparation of the solution known as "dried polio cord." Another spinal cord was removed from a healthy, normal monkey and dried similarly in a desiccator, and the solution prepared from it was designated as dried normal cord. In addition to these three solutions, two others were prepared in the routine manner, i. e., one from pooled, glycerinated, poliomyelitic monkey cords, and the other from a glycerinated normal monkey cord.

TABLE 6.—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults to Preparation from Monkey Spinal Cords Preserved by Various Methods* *

Name	Age, Years	Interval Since Onset of Paralysis	Pooled Glycerin Polio Cords		Fresh Polio Cord		Dried Polio Cord		Dried Normal Cord		Glycerinated Normal Cord	
			6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.	6 Hrs.	24 Hrs.
Ko.	16	14	0	0	0	0	++	++	+	0	0	0
Th.	15	13	0	0	0	0	++	++	0	0	0	0
Ba.	21	5	0	0	+	0	++	+	0	0	0	0
Ke.	16	1	0	0	0	0	0	0	0	0	0	0
Hu.	14	6	0	+	+	+	++	+++	+	0	+	0
Cr.†	17	5	0	0	0	0	++	+	0	0	+	0
Kea.	9	7	0	0	0	0	++	+	0	0	0	0
Co.‡	16	15	0	0	0	0	+	+	0	0	0	0
Ki.	17	10;16	0	0	0	0	±	++	0	0	0	0
Ot.	21	1	0	0	0	0	+	++	0	0	0	0
Bu.‡			..	..	..	..	0	0	0	0		
Va.†			..	..	..	..	+	±	0	0		
Fo.		No history	..	..	..	..	0	++	0	0		
Kl.†		of polio-	..	..	..	..	0	0	0	0		
Cu.		myelitis	..	..	..	..	0	++	0	0		
De.			..	..	..	..	+++	+++	+	0		
Sch.			..	..	..	..	++	++++	++	++		

* See table 2 for interpretation of signs.
† Serum neutralized virus in vitro.
‡ Serum failed to neutralize virus in vitro.

Within four days after their preparation, the solutions were injected into seven normal adults and ten persons convalescing from poliomyelitis, many of whom had been used in previous tests. When one compares the three "polio" preparations (table 6), one finds that only one of the ten convalescents gave a slightly positive reaction to the glycerinated "polio" cords and the fresh "polio" cord, respectively, whereas nine of the ten convalescents and five of the normal persons reacted more or less strongly to the dried "polio" cord. Although, with one exception, there were, at twenty-four hours, no positive reactions with any of the normal cord preparations, it is difficult to regard the results obtained with the dried "polio" cord as evidence of an allergic response to the virus, since no such reactions were obtained with the two other "polio" preparations. There is, of course, a possibility that primarily toxic substances originating from the poliomyelitic lesions were present in the dried polio cord in unusual quantities, in view of the fact that certain

toxic factors have recently been described by Toomey [4] in the stool and urine of patients with poliomyelitis. However, similarly acting toxic substances had been derived from normal cords as well in other tests. It is for this reason that no single normal cord preparation can properly constitute a control.

7. Skin Reactions with Concentrated Preparations Derived from Poliomyelitic and Normal Monkey Cords.—This test was conducted for the purpose of observing the reactions which would be elicited by purified and concentrated preparations. A method developed by one of us (A. B. S.[5]) enabled a partial purification and concentration of the virus. The solution prepared for this test was sufficiently potent (before heating) so that only 0.0003 cc. produced typical poliomyelitis in a monkey; it was apparently protein free, gave negative biuret, xanthoproteidic and ninhydrin reactions and contained only 0.04 mg. of nitrogen per cubic centimeter. For control, the spinal cords were removed from four healthy, normal monkeys and passed through precisely the same procedures for purification and concentration to which the poliomyelitic cords were submitted.

One-tenth cubic centimeter of each of the concentrated solutions was injected intracutaneously into four normal volunteers. The injections were attended by a great deal of pain which lasted only as long as the solution was being forced in from the syringe. Secondary sodium phosphate (Na_2HPO_4), which was used for extraction in the process of purification, gives similar intense pain on intracutaneous injection, and since small amounts of it might have remained in spite of the prolonged dialysis of the solutions, one hundred and fiftieth molar Na_2HPO_4 was injected as an additional control. The reactions (table 7) to the preparations derived from both the poliomyelitic and the normal cords were the most severe of any seen in the various tests; marked edema and erythema occurred, which at twenty-four hours was, on the average, about 40 mm. in diameter. That these reactions were not due to Na_2HPO_4 only is evident from the comparatively slight and transitory effect of the salt alone, and from the fact that after further dialysis of these solutions, reactions of the same intensity were produced on reinjection. The nature of the substance responsible for these particular reactions is unknown, the normal cord control having eliminated the virus as a factor. Although the final solutions were sterile, neither aseptic nor antiseptic conditions prevailed at the various stages of their preparation, and contamination

4. Toomey, J. A.: Presence of a Specific Toxic Factor in the Stools and Urines of Poliomyelitis Patients, Proc. Soc. Exper. Biol. & Med. **29**:866, 1932.

5. Sabin, A. B.: Experiments on the Purification and Concentration of the Virus of Poliomyelitis, J. Exper. Med. **56**:307, 1932.

with organisms in the air occurred; it is, therefore, not improbable that certain soluble bacterial products may be contained in them. However, whether soluble bacterial substances or spinal cord decomposition products are responsible for these reactions is not clear. Tests with suspended strips of the uterus of guinea-pigs revealed no histamine-like bodies.

SUMMARY AND COMMENT

The tests reported in this article were begun with the object of determining whether or not persons who are resistant to poliomyelitis would react differently to an intracutaneous injection of heat-inactivated virus from those who are known to be relatively more susceptible. Groups of adults and children who had no history of poliomyelitis were tested and compared with groups of persons convalescing from polio-

TABLE 7.—*Skin Reactions to Concentrated Preparations Derived from Poliomyelitic and Normal Monkey Cords*

Name	Age, Years	Partially Purified and Concentrated: Monkey Polio Virus, Reaction in Mm.	Partially Purified and Concentrated: Normal Monkey Cord, Reaction in Mm.	M/150 Na_2HPO_4, Mm.: 6 Hours	M/150 Na_2HPO_4, Mm.: 24 Hours
G. O.	18	45 × 35	50 × 40		
L. E.	21	40 × 30	55 × 45		
S. A.	26	30 × 30	50 × 40	20 × 15	10 × 10
B. O.	27	35 × 30	40 × 30	20 × 20	12 × 12

myelitis, among whom the interval since the onset of paralysis varied from four days to twenty-four years. The solutions used in these tests were sterile, heat-inactivated extracts derived from poliomyelitic monkey and human spinal cords and, for control, from the spinal cords of healthy, normal monkeys.

In some of the tests certain normal adults and persons convalescing from poliomyelitis gave positive, delayed (maximum development in from eighteen to twenty-four hours) skin reactions with preparations containing heat-inactivated virus and no reactions with similar preparations of normal cords, which appeared at first like a specific allergic response of persons who are resistant to poliomyelitis. However, after more tests had been conducted many preparations were encountered which, in spite of the fact that they were definitely potent as far as their content of heat-inactivated virus was concerned, failed to give any positive reactions. This observation naturally threw considerable doubt on the interpretation of the positive skin reactions as manifestations of specific, cutaneous allergy to the heat-inactivated virus; this doubt was further strengthened when it was found that certain preparations derived from normal cords sometimes gave positive delayed reactions

which were indistinguishable from those produced by heat-inactivated virus. It was thus evident, first, that no single normal cord preparation could be regarded as a proper control, and second, that toxic substances which give delayed skin reactions may be present in certain preparations of either normal or poliomyelitic spinal cords. Whether these toxic substances are of bacterial or of autolytic origin is not clear.

In view of the foregoing facts, there is at the present time no definite evidence for the existence of cutaneous allergy to the heat-inactivated virus of poliomyelitis in human beings, although such a possibility is not conclusively eliminated. Hence there is no basis for a skin test which would differentiate between susceptibility and resistance to the disease. Whether or not unheated virus may act differently in this respect is not known and must await the results of further investigations, which are naturally fraught with certain difficulties and remote dangers.

The medical staffs of the New York State Reconstruction Home at Haverstraw, N. Y., and the Willard Parker Hospital, New York, cooperated and assisted in this work.

EXCRETION OF NITROGEN BY OBESE PATIENTS ON DIETS LOW IN CALORIES, CONTAINING VARYING AMOUNTS OF PROTEIN

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In planning reducing diets for obese patients, the aim should be to facilitate the loss of stored fat without damaging the body structure. Older investigators [1] advocated high protein diets, but did not agree on the effects of such diets on nitrogen equilibrium. Mason [2] expressed the belief that it is unnecessary to maintain obese patients in nitrogen equilibrium, since serious losses of nitrogen do not occur. More recently [3] he has pointed out the strong tendency of such patients to conserve nitrogen, and he stated that patients who lose weight most rapidly also lose more nitrogen per day. Strang, McClugage and Evans [4] observed early small losses of nitrogen and later an equilibrium when small quantities of carbohydrates were added to low caloric diets.

Because of the rather prevalent view among clinicians that undernutrition subjects the body to bacterial invasion and overnutrition protects against infections, it is important to study the excretion of nitrogen in the obese patient on low and on high protein diets which are below his caloric requirements. Such a study should yield information of clinical value.

EXPERIMENTAL METHODS

Handling the Patient.—The patients were hospitalized during the experimental period, and their meals were served from a special diet kitchen. Some were "bed patients;" others were "ambulatory." They were weighed each morning before breakfast under standard conditions.

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1. Howard, C. P.: Obesity, in Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, p. 195. Dapper, Carl: Ueber Entfettungskuren, Arch. f. Verdauungskr. **3**:1, 1897. Hirschfeld, F.: Ueber den Eiweissverlust bei Entfettungskuren, Berl. klin. Wchnschr. **31**:621, 1894.

2. Mason, E. H.: Treatment of Obesity, Canad. M. A. J. **14**:1052, 1924.

3. Mason, E. H.: Studies upon Obesity: Source of Heat During Periods of Reduction, J. Clin. Investigation **4**:93, 1927.

4. Strang, J. M.; McClugage, H. B., and Evans, F. A.: Nitrogen Balance During Dietary Correction of Obesity, Am. J. M. Sc. **181**:336, 1931.

The urine was preserved in the icebox and analyzed daily for total nitrogen (macro-Kjeldahl), creatinine (Folin[5]), p_H (LaMotte Comparator[6]) and specific gravity. The fecal nitrogen was estimated as ten per cent of the food nitrogen. Analysis of the feces was not made.

Measuring the Energy Requirements.—It has been generally accepted that the basal requirements of the obese patient, measured in the usual way and expressed as a function of the surface area, is normal. Recently, Evans and Strang[7] suggested that the obese patient should be analyzed into a body machine, the size of which is expressed in the ideal body weight as determined by the age, height and sex factors, and into an extracorporeal mass of fat. This machine, with its surface area reduced by the exclusion of the fat, is the unit to which they estimate the energy should be supplied.

The agreement between metabolic rate and surface area in mammals of different sizes is so close that it seems unwise to deviate from this established principle of measuring the energy requirements. The basal rates of the subjects were observed repeatedly and found within the normal limits of persons of the same surface area, sex and age. The caloric value of the diets, therefore, is expressed as a percentage below this normal basal, as basal minus 30 per cent.

Diets.—The values of the foods were computed from the analyses as published in Bulletin 28 of the United States Department of Agriculture.[8] In estimating the calories derivable from a diet, the caloric value of proteins and carbohydrates was placed at 4 and of fats at 9. The diets first used contained 90 Gm. of protein and quantities of carbohydrate and fat sufficient to make up the desired calories. For convenience this is called a high protein diet. In reality it contains only an average quantity of protein. Many of the patients weighed between 100 and 150 Kg., and on this basis the protein of the diet would vary between 0.6 and 0.9 Gm. per kilogram of body weight. It is difficult to estimate the energy expended by these patients in the course of the day. They were ambulatory, some quite active and others sedentary. It seems safe to assume that the ambulatory patients were using basal plus 20 per cent calories. The diets ranged between basal minus 30 per cent and basal minus 40 per cent. On such an assumption, the patients would derive from 40 to 50 per cent of their daily energy from the body.

5. Folin, O.: On the Determination of Creatinine and Creatine in Urine, J. Biol. Chem. **17**:469, 1914.

6. Lamotte Chemical Company, Baltimore. Hawk and Bergeim: Practical Physiological Chemistry, ed. 8, Philadelphia, P. Blakiston's Son & Co., 1923, p. 709.

7. Evans, F. A., and Strang, J. M.: The Treatment of Obesity with Low Caloric Diets, J. A. M. A. **97**:1063 (Oct. 10) 1931.

8. Atwater, W. O., and Bryant, M. S.: U. S. Dept. Agric., Bull. 28, 1906.

The carbohydrate varied between 60 and 150 Gm. as the calories increased from 1,024 to 1,600. The patients on the diets that contained less than 30 Gm. of butter were given either oscodal tablets or 5 Gm. of cod liver oil to supply vitamins A and D.

Plan of the Experiment.—On entering the hospital, the patients, during a preliminary period, received diets containing their basal requirements, which included 90 Gm. of protein. After one or two weeks the calories were reduced to the desired level, with 90 Gm. of protein. In the earlier experiments collection periods of urine for from five to seven days were introduced at stated intervals. In the latter experiments the urine was collected daily during the extire period. The diet contained basal minus 30 per cent calories for six weeks. At the end of this time the basal requirements were refigured and a diet given which contained 13.5 Gm. of protein and basal minus 30 per cent calories for a period of six weeks. This period was followed by another one of six weeks, during which the patients received 90 Gm. of protein and basal minus 30 per cent calories.

RESULTS

Positive Nitrogen Balance on Diets with 90 Gm. of Protein.—Table 1 shows that under the conditions of the experiment, on a diet containing 90 Gm. of protein, with calories from 40 to 50 per cent below the actual requirements and from 30 to 40 per cent below basal requirements, and ambulatory activity, the patients remained in positive nitrogen balance. The retention of nitrogen was definite; the majority of values were between 1 and 2 Gm. per day, with higher values of 2.2 Gm. (H. H.), 2.75 Gm. (M. M.) and 5.05 Gm. (E. H.). In the experimental periods, which are starred in the table and which followed periods of low protein feeding, the retention of nitrogen (2.29, 4.67 and 5.65 Gm. daily for forty-two days) was more striking.

Mason [2] reported experiments on five patients whose diets contained from 23 to 49 Gm. of protein, from 10 to 62.5 Gm. of carbohydrate, from 4.9 to 15.4 Gm. of fat and from 202 to 650 calories. All of these patients had negative nitrogen balances for the entire experimental period, but toward the close of the period one patient was in positive nitrogen balance, and the remainder were in only slight negative balances. Strang, McClugage and Evans [4] fed patients diets quite similar to those of Mason, and they noted an early loss of nitrogen which ceased when the carbohydrate in the diets was raised to 20 Gm. The diets used by these investigators were much lower in protein and calories than those reported in table 1.

It was of interest to note whether patients on these diets had a negative balance at any time, and to see what significance is to be attached to such periods of negative balance. In table 2 an analysis is presented of the experiments in which sporadic periods of negative

TABLE 1.—*Positive Nitrogen Balance of Obese Patients*

Patient	Experimental Days	Weight, Kg.	Age	Diet		Nitrogen, Gm.		Length of Period, Days	Activity
				Protein, Gm. per Day	Calories per Day	Balance in Period	Balance per Day		
S. C.	8-44	91.8	31	14.5	B — 30% 1,174	56.554	1.61	35	Ambulatory
S. C.	44-79	82.7	31	14.5	B — 30% 1,144	23.815	0.68	35	Ambulatory (more exercise)
M. H.	1-29	120.2	39	14.51	B — 30% 1,425	9.257	0.33	28	Rest in bed
M. H.	68-103	107.3	39	7.98	B — 42% 1,002	39.873	1.14	35	Rest in bed
H. K.	19-61 70-77	167.6 155.0	33	20.46	B — 30% 1,575	58.95	1.2	49	Sedentary
H. K.	1-53	116.4	35	14.4	B — 30% 1,900	75.033	1.53	49	Sedentary
N. P.	15-57	143.8	40	14.48	B — 30% 1,441	26.029	0.62	42	Ambulatory
N. P.*	100-141	125.0	40	14.51	B — 30% 1,350	94.290	2.289	41	Ambulatory
N. P.	141-183	119.5	40	14.43	B — 30% 1,317	0.432	0.010	42	Ambulatory
N. P.	190-232	113.4	40	14.48	B — 30% 1,297	—0.022	—0.0005	42	Ambulatory
N. P.	232-274	106.8	40	14.43	B — 30% 1,266	0.210	0.005	42	Ambulatory
M. M.	8-50	118.0	39	14.43	B — 30% 1,313	36.226	0.86	42	Ambulatory
M. M.*	92-134	100.1	39	14.37	B — 30% 1,220	196.199	4.67	42	Ambulatory
M. M.	135-170	94.3	39	14.45	B — 30% 1,172	96.303	2.75	42	Ambulatory
L. M.	8-50	127.3	44	14.51	B — 30% 1,360	55.086	1.31	42	Sedentary
L. M.*	78-120	112.2	44	14.5	B — 30% 1,386	237.542	5.65	42	Sedentary
E. L.	15-40	121.1	41	14.35	B — 30% 1,465	43.750	1.75	25	Quite active
Y. B.	22-43	77.4	39	14.37	B — 33% 1,054	74.335	3.54	21	Rest in bed
H. H.	81-88	82.7	17	14.4	B — 25% 1,278	15.655	2.2	7	Ambulatory
E. H.	73-101	88.1	33	14.4	B — 30% 1,162	141.416	5.05	21	Active
E. H.	15-43	97.7	33	14.4	B — 30% 1,201	41.035	1.95	21	Active
M. F.	1-8 14-21	113.0	41	14.4	B — 40% 1,014	21.69	1.55	14	Ambulatory
L. R.	2-16 24-31	128.1	27	14.4	B — 30% 1,360	6.073	0.289	21	Ambulatory
L. R.	35-42	124.1	27	14.4	B — 43% 1,101	10.789	1.541	7	Ambulatory

* Present period immediately preceded by diet low in protein.

balance occurred. In this table, the character of diet and its duration during the preliminary period are shown. In the experimental period the weeks during which the balance was positive and the weeks during which it became negative are shown. In the last column, the negative balance per day is expressed in grams. It should be noted that in six of the eleven experiments the balance was positive at all times. In the other five experiments, there was a total of eight of forty-three weeks during

TABLE 2.—*Negative Nitrogen Balance of Patients in Table 1 (Basal, 30 Per Cent Calories; Protein, 90 Gm.)*

	Preliminary Period		Experimental Period			
					Negative Balance	
Patient	Type of Diet	Duration, Weeks	Calories	Positive Balance, Weeks	Weeks	Gm. a Day
S. C.	Basal N 14.5	1	B — 30% 1,174	1:2:3:4:6:7:8:9:10	5	0.031
E. L.	Basal N 14.5	2	B — 30% 1,465	1:2:3:4		
M. M.	Basal N 14.3	1	B — 30% 1,313	1:2:4:6	3	1.627
					5	0.132
M. M.	B — 30% N 2.19	6	B — 30% 1,220 1,172	1:2:3:4:5:6:7:8:9: 10:11		
L. M.	Basal N 14.4	1	B — 30% 1,360	1:2:3:4:5:6		
L. M.	B — 30% N 2.2	4	B — 30% 1,386	1:2:3:4:5:6		
N. P.	Basal N 14.3	2	B — 30% 1,014	1:2:3:5:6	4	0.945
N. P.	B — 30% N 2.2	6	B — 30% 1,350	1:2:3:4:5:6		
M. H.	Uncontrolled	..	B — 30% 1,425 1,002	2:3:4:5:6:7:8:9:10: 11:12:13:14	1	1.056
H. K.	Basal N 20.46	2	B — 30% 1,575	2:3:4:7	1	2.820
					5	0.490
					6	2.740
H. K.	Basal — 20% Protein 90 (at home)	Several months	B — 30% 1,328	1:2:3:4:5:6:7		

which there was negative balance. In three of the eight weeks the balance was so slight that the patient might be considered as being in equilibrium. This leaves five weeks scattered irregularly throughout the total eighty-three experimental weeks during which the balance was negative, a percentage of 6. The absence of any regularity in the location of these periods and the lack of correlation between the negative balance and the loss of weight would indicate that the loss of nitrogen is not predictable and is not essential to the loss of weight. It is probably related in some way to adjustments in the deposit nitrogen.

Negative Nitrogen Balance on Diets with 90 Gm. of Protein.—Table 3 summarizes the records of the patients in whom negative nitrogen balances developed. A study of this table shows that there are only four experiments (E. G., L. D., N. P. and N. P.*) of sufficient duration to be comparable with those summarized in table 1. One of these patients (L. D.) was confined to bed. Although her negative balance was small, it probably would have been larger had she been ambulatory. One patient (E. G.) was reasonably active (ambulatory), but not more so than many in table 1. Her negative balance (—2.76) was definite. N. P. had an interesting case. At the age of 36 and while on diets of basal minus 48 per cent and basal minus 42 per cent calories,

TABLE 3.—*Negative Nitrogen Balance of Obese Patients (Protein, 90 Gm.: Submaintenance Diets)*

Patient	Experimental Days	Weight, Kg.	Age	Diet		Nitrogen Balance		Length of Period, Days	Activity
				Protein, Gm.	Calories	Per Period	Per Day		
B. B.	6-13	114.3	35	14.4	B — 31% 1,302	—11.95	—1.71	7	Ambulatory
H. M.	6-13	90.7	30	14.4	B — 31% 1,208	—12.15	—1.74	7	Ambulatory
L. T.	5-12	101.3	40	14.27	B — 39% 1,023	—17.84	—2.26	7	Ambulatory
E. G.	1-29	139.5	25	14.4	B — 30% 1,400	—77.19	—2.76	28	Ambulatory
L. D.	49-56 71-99	88.1	52	14.4	B — 30% 1,135	— 2.47	—0.07	35	Rest in bed
D. S.	1-8	82.3	25	15.66	B — 30% 1,218	— 3.22	—0.40	8	Laboratory work
N. P.	1-8 9-73	127.7	36	14.4	B — 48% 1,014	—245.70	—3.51	70	Sedentary
N. P.*	107-156	99.8	36	14.27	B — 42% 1,023	—60.61	—1.23	49	Sedentary

* Followed a period of low protein.

negative nitrogen balance developed. At the age of 40, when her weight was approximately the same, and while on a diet of basal minus 30 per cent calories, she remained in positive nitrogen balance, as shown in table 1. The question arises: Is this difference in balance attributable to a difference (18 and 12 per cent, respectively) in the caloric value of the diets, or to changes within the patient between the years of 36 and 40? The subjects of the first three experiments (B. B., H. M. and L. T.) had been dispensary patients, and as such they lost weight remarkably well. They would not consent to a long period of hospitalization, so were admitted for two weeks. Prior to admission, they had been living on a quantitative diet and had weighed their food daily so that the transfer to the hospital involved little change in diet. During the first week they were in the hospital, the urine was discarded, and

the analytic results of the urine collected during the second week are shown in table 2.

It is evident that the number of patients in whom negative balances developed while on diets of this character is much smaller than the

TABLE 4.—*Summary of Results on Low Protein Diets*

Name	Weight, Kg.	Age	Calories	Length of Time on Diet, Days	Intake of Nitrogen, Gm.	Daily Nitrogen in Urine Averaged for Seven Days, Gm.	Daily Total Nitrogen (Urine N_2 + 10% Intake N_2) Seven Days, Gm.	Daily Nitrogen Balance, Averaged for Seven Days, Gm.	Experimental Days	Activity
S. C.	82.7 to 78.4	31	B — 30% 1,144	42	2.11	3.652 3.978 3.846 4.437 3.803 4.016	3.86 4.19 4.06 4.65 4.01 4.23	—1.76 —2.08 —1.95 —2.53 —1.90 —2.12	42	Ambulatory
H. K.	154.3 to 147.7	33	B — 26% 1,574	14	2.02	7.82 4.17	8.02 4.37	—5.32 —2.36	12	Sedentary
	110.0 to 102.7	35	B — 29% 1,315	45	2.05	5.18 3.68 3.47 3.63 2.38 3.13	5.38 3.89 3.67 3.83 2.58 3.33	—3.32 —1.84 —1.63 —1.78 —1.54 —1.28	42	Sedentary
H. H.	83.8 to 83.9	17	B — 32% 1,201	11	2.24	5.10	5.33	—3.09	5	Ambulatory
M. M.	108.1 to 104.5	39	B — 30% 1,233	42	2.19	4.25 2.98 2.64 3.68 3.11 4.19	4.47 3.20 2.86 3.897 3.33 4.40	—2.28 —1.01 —0.66 —1.71 —1.14 —2.21	42	Ambulatory
L. M.	118.1 to 112.2	44	B — 30% 1,310	32	2.20	3.95 2.73 2.58 3.20	4.17 2.95 2.80 3.42	—1.97 —0.75 —0.589 —1.22	28	Ambulatory
N. P.	108.9 to 100.2	36	B — 42% 1,067	32	2.02	5.49 4.51 3.47 4.91	5.69 4.71 3.68 5.12	—3.68 —2.70 —1.66 —3.10	31	Ambulatory
	93.6 to 85.4	36	B — 39% 1,067	46	2.02	6.85 3.91 5.12 4.61 3.68 4.19	7.05 4.12 5.33 4.82 3.89 4.40	—5.03 —2.15 —3.31 —2.80 —1.87 —2.38	45	Ambulatory
	134.8 to 125.2	40	B — 30% 1,365	43	2.20	3.67 3.96 2.67 2.95 2.01 1.36	3.89 4.18 2.89 3.17 2.23 1.58	—1.69 —1.98 —0.69 —0.97 —0.03 +0.62	42	Ambulatory

number in whom positive balances developed. This may be a characteristic reaction of these particular subjects to submaintenance diets containing an adequate quantity of protein. The significance of this point will be discussed later.

Negative Balance on Low Protein Diets.—Since patients showed a marked tendency to conserve nitrogen on diets containing 90 Gm. of protein, it was important to know the effect of diets low in protein (from 12.5 to 14 Gm.). In table 4 the results of such studies are summarized. In column 7, the daily excretion of nitrogen, averaged over seven days throughout the experiments, is shown. Column 9 shows the daily negative balance computed in the same way. Again one is struck by the frugality of protein metabolism under this extremely low intake of nitrogen.

Nitrogen Minimum.—Since the excretion of nitrogen was low, it was decided to compare it with the values for "wear and tear nitrogen" or "nitrogen minimum." A patient (N. P., table 5) who had been cooperative was selected for this study. A palatable diet, low in nitrogen and containing an excess of calories (basal plus 50 per cent), was used. Her requirements under the condition of hospital life could not have exceeded basal plus 30 per cent. During the first two days the diet consisted of 400 Gm. of starch and 300 Gm. of cream, but this was abandoned because it was unpalatable. For the next four days the diet consisted of 200 Gm. of 36 per cent cream, 100 Gm. of bananas, 200 Gm. of lemon juice, 83 Gm. of butter, 100 Gm. of boiled potato, 20 Gm. of dry rice and 156 Gm. of dextrose. During the remaining nine days the cream in the diet was raised to 300 Gm., and the other articles remained the same. From the table (column 2) it will be noted that there were some variations in the intake of nitrogen. The earlier differences are accounted for by the changes in the character of the food at the end of the second and the sixth days. Total estimations of nitrogen were made on each new bottle of cream, and some variations were found. This factor alone accounts for the differences in the intake of nitrogen during the last nine days.

Variations in fat also must have occurred in the samples of cream, but these were not estimated. Since the calories were evidently in excess of the patient's requirements, such variations were not considered important. There are in this experiment the standard conditions for the determination of the nitrogen minimum. It may be noted (column 3, table 5) that after the sixth day the urinary nitrogen dropped below 3 Gm., and reached a value of 2.24 Gm. on the fifteenth day. These values are close to those reported by Thomas and others[9] but not so low as those (1.76 Gm.) obtained by Deuel, Sandiford, Sandiford and Boothby[10] in an experiment lasting a much longer time.

9. Thomas, Karl: Ueber das physiologische Stickstoffminimum, Arch. f. Physiol. (Supp. Bd., 1910), p. 249. Landegren, Ernest: Untersuchungen über die Eiweissumsetzung der Menschen, Skandinav. Arch. f. Physiol. **14**:112, 1903.

10. Deuel, H. J., Jr.; Sandiford, I.; Sandiford, K., and Boothby, W. M.: A Study of the Nitrogen Minimum, J. Biol. Chem. **76**:391, 1928.

In the next experiment the nitrogen in the diet was 2.2 Gm. (estimated from bulletin 28 [8]) and the calories were basal minus 30 per cent. The first fourteen days of this period followed a period during which the diet consisted of 90 Gm. of protein and basal minus 30 per cent calories. The behavior of the nitrogen (column 4, table 5) is quite similar in the two experiments. In the fifth column, the values for the excretion of nitrogen during the fourteen days from the twenty-eighth to the forty-second day of the same experiment are shown. On these days the values reached the levels recorded by Smith [11] and by Deuel, Sandiford, Sandiford and Boothby [10] for a normal subject. It should be emphasized at this point that the caloric value

TABLE 5.—*Nitrogen Excretion of Obese Patients Under Specific Nitrogen Hunger and Varying Number of Calories (Nitrogen Minimum)*

Weight.....	98.4 Kg.		134.5 Kg.	129.5 Kg.	98.4 Kg.
Diet.....	B + 50%		B — 30%	B — 30%	B — 61.5%
COH.....	(app.) 243.3		163.0	163.0	149.6
Nitrogen.....	(app.) 1.7		2.201	2.201	0
Calories.....	2,630		1,905	1,565	598.4
On diet.....	1-15 days		1-14 days	28-42 days	1-10 days
Days	Intake of Nitrogen, Gm.	Urine Output of Nitrogen, Gm.	Urine Output of Nitrogen, Gm.	Urine Output of Nitrogen, Gm.	Urine Output of Nitrogen, Gm.
1	0.723	5.90	5.62	1.48	7.66
2	0.723	3.49	5.23	0.33	6.81
3	1.528	5.10	4.37	0.97	4.12
4	1.528	4.05	3.33	3.996	3.77
5	1.528	3.25	3.42	2.13	4.51
6	1.478	3.64	1.60	2.53	4.31
7	1.725	2.89	2.13	2.62	4.17
8	1.586	2.84	3.26	1.26	3.77
9	1.586	2.40	2.70	0.93	4.05
10	1.619	2.98	1.47	1.97	3.89
11	1.619	2.83	....	1.66	
12	1.821	3.37	....	1.50	
13	1.821	3.05	4.94	1.17	
14	1.725	2.76	3.76	1.02	
15	1.573	2.24	4.54	1.53	

of this diet is approximately 40 per cent below the actual energy expended by the patient.

A third experiment is shown in column 6 of table 5. In this case the patient was given 200 Gm. of lemon juice and 130 Gm. of dextrose, making a total of 148.6 Gm. of carbohydrate and 598.4 calories per day. This diet was approximately from 67 to 70 per cent below the actual energy requirements of the patient. Although the experiment was continued for only ten days, the nitrogen values are of the same order as those noted in the other experiments. Whether by a continuation of the experiment over a period of fourteen days or more we would have arrived at lower values is not evident and is not important. It is quite evident that an obese patient may arrive at or

11. Smith, Millard: Minimum Endogenous Nitrogen Metabolism, J. Biol. Chem. **68**:15, 1926.

approximate closely the nitrogen minimum in the urine providing the intake of nitrogen is reduced to the proper level and sufficient carbohydrate is given to meet his requirements for this food. It is not necessary, as in the case of the normal subject, to supply him with an excessive caloric intake. The stored fat is readily available and meets any caloric deficit that may arise.

Excretion of Creatinine.—The daily excretion of creatinine was not a constant quantity even on a meat-free diet. The data shown in table 6 were obtained from seven women and one man. These patients were eating diets containing basal minus 30 per cent calories, with the exception of M. H., who was on basal minus 48 per cent calories. The meat-

TABLE 6.—*Daily Excretion of Creatinine on Reducing Diets*

N. P.		M. M.		L. M.		M. H.		S. C.		H. K.		M.D.†		E. L.
14.4	2.2	14.4	2.19	14.4	2.2	14	7.98	14.4	2.11	14.4	2.04	14.4	2.176	14.4
0.467	0.512	0.588	0.278	0.443	0.288	0.583	0.351	0.589	0.488	0.622	0.512	0.537	0.576	0.565
0.526	0.496	0.489	0.388	0.440	0.427	0.474	0.367	0.605	0.484	0.529	0.526	0.456	0.604	0.594
0.485	0.510	0.511	0.427	0.575	0.362	0.560	0.447	0.484	0.457	1.049	0.509	0.528	0.539	0.651
0.536	0.464	0.412	0.374	0.441	0.326	0.501	0.423	0.708	0.540	0.941	0.592	0.518	0.671	0.800
0.499	0.522	0.400	0.356	0.414	0.214	0.624	0.449	0.480	0.436	0.562	0.502	0.523	0.544	0.821
0.427	0.456	0.497	0.351	0.477	0.519	0.451	0.455	0.514	0.452	0.560	0.374	0.493	0.726	0.682
0.719	0.443	0.522	0.408	0.448	0.300	0.572	0.323	0.456	0.485	0.679	0.529	0.516	0.549	0.628
0.540	0.504	0.535	0.445	0.441	0.235	0.527	0.479	0.504	0.473	0.599	0.462	0.491	0.457	0.700
0.532	0.463	0.579	0.464	0.501	0.439	0.525	0.463	0.418	0.454	0.656	0.498	0.419	0.531	0.687
0.602	0.425	0.368	0.478	0.530	0.241	0.539	0.381	0.577	0.575	0.672	0.434	0.561	0.621	0.522
0.527	0.265	0.927	0.507	0.524	0.248	0.519	0.423	0.473	0.480	0.648	0.450	0.527	0.566	0.655
0.526	0.342	0.715	0.464	0.510	0.263	0.534	0.420	0.562	0.540	0.445	0.568	0.500	0.499	0.711
0.518	0.720	0.579	0.335	0.501	0.271	0.425	0.332	0.571	0.444	0.562	0.469	0.542	0.492	0.678
0.762	0.503	0.498	0.507	0.512	0.410	0.571	0.424	0.476	0.455	0.554	0.457	0.551	0.597	0.725
Mean 0.547	0.473	0.544	0.413	0.482	0.326	0.529	0.409	0.530	0.483	0.648	0.498	0.514	0.569	0.693
MD. 0.063	0.065	0.096	0.064	0.039	0.078	0.040	0.042	0.062	0.0305	0.107	0.049	0.030	0.047	0.077
MD.% 11.4	13.7	17.4	15.6	8.1	23.9	7.5	10.3	11.6	6.3	16.5	9.8	5.8	8.2	9.7

* Diets were basal—30 per cent with exception of M. H., on basal—48 per cent.
† Experiment began in case M. D. immediately after institution of diet. In all other cases experiment began two weeks after institution of diet.

containing diets had nitrogen values of 7.98 and 14.4 Gm. The meat-free diets had values of 2.1 and 2.2 Gm. of nitrogen.

The values of the excretion of creatinine are given for fourteen days. The mean (M), mean deviation (MD) and mean deviation expressed in percentage (MD %) appear at the bottom of the table. These periods of fourteen days (except patient M. D.; protein, 14.4 Gm.) began between the fourteenth and twenty-first day after the patient had begun the indicated diet. It was hoped in this way to avoid any confusion that might arise from variations in the "deposit nitrogen." It may be assumed that the creatine of the meat varied between 0.3 and 0.5 Gm. (Andrew Hunter[12]), which, according to Benedict and Osterberg,[13] would yield a maximum creatinine of from 0.09 to 0.15

12. Hunter, Andrew: Creatine and Creatinine, Monograph on Bio-Chemistry, New York, Longmans, Green & Co., 1928, p. 114.

13. Benedict, S. R., and Osterberg, E.: Studies in Creatine and Creatinine Metabolism, J. Biol. Chem. **56**:229, 1923.

Gm. if all of the creatine eaten were retained within the body. If only 60 per cent were retained, as their figures would indicate, then the creatinine derived from this source would vary between 0.054 and 0.09 Gm.

From an examination of the means it will be noted that the excretion of creatinine was somewhat higher on the meat-containing diet. The case of M. D. forms an exception to this rule. However, the fourteen days (being the only ones available) selected for this study were the first fourteen days immediately following the institution of the diet containing 14.4 Gm. of nitrogen, and for this reason they are not strictly comparable.

The differences in the excretion of creatinine on creatine-free diets (low protein) and creatine-containing diets may be due not only to the actual amount of creatine in the diet, but also to the prolonged use of a low protein, creatine-free diet, which Ringer and Raiziss [14] have previously reported as causing a lowering of the excretion of creatinine.

Reference to the mean deviations expressed in percentages will show that the daily variations may be considerable. In five of fifteen experiments, the mean deviation was above 12 per cent, and in the other ten below 12 per cent. If the volume of urine and the total nitrogen are examined on the days on which there were large variations in creatinine, they will be found to vary independently, indicating that there were periods of retention of creatinine followed by periods of increased excretion. These findings in obese patients agree with those reported for normal subjects by McLaughlin and Blunt [15] and by others.[12]

Excretion as Affected by Loss of Weight.—Table 7 summarizes the data on excretion of creatinine during the experimental period. Losses in body weight varying between 66.9 and 6.8 Kg. are recorded. The mean deviation, expressed in percentage, shows that no significant changes in creatinine occurred as the result of loss in body weight. This is in keeping with the findings of McClugage, Booth and Evans.[16]

COMMENT

The excretion of nitrogen of the obese person differs strikingly from that of the normal subject. The majority of obese persons remain in positive balance when from 50 to 90 Gm. of protein is fed

14. Ringer, A. L., and Raiziss, G. W.: Excretion of Creatinine by Human Individuals on a Prolonged Creatinine Free Diet, J. Biol. Chem. **19**:487, 1914.

15. McLaughlin, L., and Blunt, K.: Some Observations on Creatinine Excretions of Women, J. Biol. Chem. **58**:285, 1923.

16. McClugage, H. B.; Booth, G., and Evans, F. A.: Creatinine Excretion in Abnormal States of Nutrition, Am. J. M. Sc. **181**:349, 1931.

even though the diet is insufficient in calories. Even on diets containing minimal quantities of nitrogen, the loss in nitrogen is small. The normal subject (Benedict and his co-workers [17]) loses nitrogen under such conditions. It is further shown that the obese patient may excrete a nitrogen minimum when the calories in his food are 40 per cent below his actual requirements. These findings indicate that the stored fat is mobile and easily shifted into the metabolizing mixture when the food is deficient in calories. Briefly, it is impossible to induce in obese persons the sequelae of undernutrition found in the normal subject provided protein and carbohydrate are fed in quantities sufficient for antiketogenesis and for meeting the "wear and tear quota" of nitrogen. The store of fat protects the body's nitrogen against demands for energy.

In the group of persons who lost nitrogen on these diets, the subjects were of the same weight and appearance as their associates. There may

TABLE 7.—*Excretion of Creatinine as Effected by Loss of Weight*

Patient	Duration of Experiment		Loss of Weight, Kg.	Creatinine Excretion		
	Weeks	Number of Analytic Weeks		Mean, Mg. of Nitrogen	Mean Deviation, Mg. of Nitrogen	Mean Deviation, per Cent
H. K. (1928)	14	14	23.2	0.530	0.040	7.6
H. K. (1930)	16	16	14.1	0.543	0.064	11.8
H. K. (1928-1930)	104	30	66.9	0.537	0.054	10.0
N. P.	56	56	56.8	0.515	0.041	7.96
L. M.	18	18	21.3	0.478	0.087	18.2
M. M.	26	26	28.9	0.498	0.059	11.8
S. C.	18	18	13.1	0.500	0.048	9.6
M. H.	15	15	16.6	0.520	0.051	9.8
M. D.	9	9	6.8	0.558	0.059	10.5

have been a greater expenditure of energy by these subjects than by their obese associates, although they were living under the same conditions, and thus the mobilization of fat may not have been sufficiently rapid to protect the nitrogen. On the other hand, the obesity defect in these persons may have been less severe, and it may be that in this respect they resembled more closely the normal person. If this is true, then this preservation of a positive nitrogen balance while eating a diet markedly deficient in calories would become a characteristic finding of persons with the obesity defect, and its appearance would have diagnostic significance.

CONCLUSIONS

1. A majority of the obese patients studied maintained a positive nitrogen balance when fed 90 Gm. of protein per day and a diet from 40 to 50 per cent below their energy requirements.

17. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, Washington, D. C., Carnegie Institution, 1919, publication no. 280.

2. In a smaller number a negative balance developed under similar conditions.

3. When the obese patient is fed from 13 to 14 Gm. of protein per day, the negative nitrogen balance is small.

4. It was shown in one case that the nitrogen minimum obtained on a diet containing 1,365 calories (which was 46 per cent below the actual requirements) was smaller than one obtained on 2,630 calories (which was 15 per cent above the actual requirements).

5. The fat constitutes a mobile supply of energy which is so easily requisitioned that starvation sequelae do not develop in the obese patient provided carbohydrate is furnished for antiketogenesis and protein for the "wear and tear quota."

6. The daily excretion of creatinine is reasonably constant, but periods of retention are succeeded by periods of increased excretion. The mean deviation calculated over periods of fourteen days often shows a variation exceeding 10 per cent.

7. The weekly variations are quite constant, and the mean deviation calculated over the period of loss of weight did not show more than a 10 per cent variation, when this loss amounted to 56.8 and 66.9 Kg., respectively. It is evident that excretion of creatinine is not affected by the loss of weight produced in this manner.

8. It was suggested that the patients in whom a negative nitrogen balance developed had a less severe obesity defect.

HISTAMINE TEST MEALS

AN ANALYSIS OF NINE HUNDRED AND EIGHTY-EIGHT CONSECUTIVE TESTS

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SAN FRANCISCO

During the past few years the growing emphasis on quantitative and biometric methods in clinical medicine has brought into question the older methods of studying gastric secretion, and numerous articles have appeared in which the attempt is made to reassess the various forms of test meal. For reasons previously exposed,[1] histamine seems the best available agent for the clinical study of gastric secretion, and the histamine test has been systematically used in this clinic for the past four years. The records of 988 tests are now available, a number that is large enough to yield conclusions more or less definitive. The present article deals with an analysis of this material.

MATERIAL

The subjects included patients with gastro-intestinal complaints, and also a large group who were subjected to the test as part of a general diagnostic study. There were a good many persons to all intents and purposes normal (table 1). The miscellaneous group includes cases of cardiovascular disease, tuberculosis, pernicious anemia, diseases of the liver and gallbladder, infestations with parasites and other diseases. There were not enough of each to justify separate analysis. The excess of male subjects is mainly due to the preponderance of this sex in the hospital clientele.

Table 2 shows the distribution by age periods. Most of the patients were between the ages of 20 and 69, and outside of this range the material is inadequate.

METHODS

The test procedure has been amply described in previous papers.[2] Briefly, the subject fasts for at least twelve hours and is examined in the basal state. A Wilkins tube is introduced into the stomach, and after withdrawal of the fasting contents 0.1 mg. of histamine (beta-iminazolylethylamine hydrochloride) per ten

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From the Department of Medicine, Stanford University Medical School.

1. Bloomfield, A. L., and Polland, W. S.: The Diagnostic Value of Studies of Gastric Secretion, J. A. M. A. **92**:1508 (May 4) 1929.

2. Polland, W. S.; Roberts, A. M., and Bloomfield, A. L.: The Chloride, Base and Nitrogen Content of Gastric Juice After Histamine Stimulation, J. Clin. Investigation **5**:611, 1928. Bloomfield and Polland.[1]

kilograms of body weight is injected hypodermically. The total secretions are then aspirated over successive ten minute periods until the flow of juice subsides (about one hour). The greatest volume of juice secreted in a ten minute period and the highest titratable acidity attained are taken as indexes of the secretory capability of the stomach and furnish the data on which this report is based. Two hundred and thirty-five of the examinations were performed by me; the others were made by members of the house staff or by specially trained technicians.

In a large series of cases the average difference between free and total acidity was found to be 10 cc. of tenth-normal hydrochloric acid per hundred cubic centimeters of gastric juice; in order to avoid duplication, therefore, only the total acidity is tabulated. Furthermore, by using total acidity it is not necessary to group all cases of "anacidity" on the zero abscissa.

TABLE 1.—*Classification of Material*

	Males	Females	Total
Normal persons	384	270	654
(Unexplained anacidity)	41	38	79
Duodenal ulcer	112	18	130
Gastric ulcer	31	5	36
Carcinoma of stomach	46	10	56
Miscellaneous	43	69	112
Total	616	372	988

TABLE 2.—*Relation of Age to Material Studied*

Age	Males	Females	Total
10-19	8	6	14
20-29	107	56	163
30-39	124	93	217
40-49	166	85	251
50-59	118	78	196
60-69	68	39	107
70-79	23	14	37
80-89	2	1	3
Total	616	372	988

NORMAL STANDARDS

Interpretation of findings in disease is obviously impossible except by comparison with sound normal standards. Polland and Bloomfield,[3] recognizing this need in the present connection, made a careful analysis of the results of histamine tests in 100 normal people. While the series was small, the wide range of acid and of volume was emphasized, as well as the tendency for the rate of secretion to fall with advancing years, a point already touched on by Bloomfield and Keefer.[4] No attempt was made to analyze separately the findings in the two sexes until the appearance of the comprehensive report of Vanzant and

3. Polland, W. S., and Bloomfield, A. L.: Normal Standards of Gastric Function, J. Clin. Investigation **9**:651, 1931.

4. Bloomfield, A. L., and Keefer, C. S.: Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness, J. Clin. Investigation **5**:285, 1928.

Alvarez and their associates.[5] In a study of 3,746 test meals (Ewald and Ewald plus histamine), they, too, found a decline of acidity in males as age increased, but there was practically no change in the females. Volume of secretion was not considered.

The group selected as "normal" for the present study included people who had no evidences of any significant disease, who were free from digestive symptoms and who on physical and laboratory examination showed no signs of disease of the gastro-intestinal tract. Patients with acute febrile conditions, with cachexia or with any disorder that presumably might derange gastric function, such as cardiac decompensation, were excluded. Patients with unexplained anacidity, however, provided they met the foregoing specifications in other ways, were accepted.

Acidity.—In table 3, the distribution by age of the highest total acidity in both sexes (normal) is shown. The most striking finding is the wide variation of acidity at all age periods, which makes it evident that no narrow standards of normality can be set up. The total range in both sexes is from 0 to 160 units of acid. On calculating the coefficient of correlation between age and gastric acidity, the results were found to be -0.236 ± 0.033 for the male subjects, a value which is significant and indicates a slight negative correlation between age and acidity, and -0.146 ± 0.041 for the female subjects, a value which is hardly significant. A comparison of the mean values for each age period shows that in the male subjects there is a definite decrease in acid with advancing years, but hardly any falling off in the older female subjects. A comparison of the two sexes also shows that the female subjects have in each decade a much lower acidity, except in the higher age group, in which the values for the male subjects decrease to the female level. These two important points have recently been emphasized by Vanzant.[5] Chart 1 shows graphically the mean total acidity in various decades.

Even if the cases of anacidity are excluded, the average total acidity falls with age in the male subjects, but it remains practically constant in the female subjects.

Volume.—In table 4, the distribution by age of the volume of secretion is shown. Here, also, there is considerable variation, but the coefficient of correlation between age and volume for the male subjects is -0.331 ± 0.031, and for the female subjects, -0.276 ± 0.038, values which are significant. It is apparent that the female subjects have a mean volume of secretion less than the male subjects for all

5. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, Joseph: The Normal Range of Gastric Acidity from Youth to Old Age, Arch. Int. Med. **49**:345 (March) 1932.

age periods, and that the secretory volume decreases appreciably from youth to old age. Chart 2 shows graphically the mean volume both with and without the cases of anacidity.

TABLE 3.—*Total Acidity in Relation to Age and Sex (Normal Persons)*

Males

Units of Acid	Age, Years								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
150-159	..	1	..	1	2	..	..	..	4
140-149	1	10	5	1	3	1	..	..	21
130-139	1	11	7	10	3	..	..	..	32
120-129	..	7	12	14	6	5	..	1	45
110-119	2	6	4	13	5	3	4	..	37
100-109	..	5	10	11	6	2	..	..	34
90-99	3	7	10	10	6	2	..	..	38
80-89	..	6	7	6	2	2	..	..	23
70-79	..	4	7	7	5	1	1	..	25
60-69	..	4	9	6	8	3	..	..	30
50-59	..	4	4	6	1	4	1	..	20
40-49	..	1	5	5	4	1	..	..	16
30-39	..	..	2	1	3	..	1	..	7
20-29	.	1	1	5	2	..	3	..	12
10-19	..	2	2	7	6	9	1	..	27
0-9	..	1	1	4	3	2	1	1	13
Total	7	70	86	107	65	35	12	2	384
Mean		101.1	91.5	86.0	80.0	67.1			
Probable error of mean		2.86	1.83	2.54	3.56	4.98			
Standard deviation		35.7	25.2	38.8	42.6	43.7			
Coefficient of variability		35.3	27.5	45.1	53.3	43.7			
Mean of 326 cases with free acid		105.9	94.4	95.2	91.1	92.0			

Females

Units of Acid	Age, Years								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
150-159	..	..	1	..	..	..	..	..	1
140-149	..	1	..	1	..	..	..	..	2
130-139	..	2	3	..	1	2	..	..	8
120-129	..	..	8	3	3	1	1	..	16
110-119	..	6	3	4	1	2	1	..	17
100-109	..	3	5	7	6	4	..	..	25
90-99	1	9	3	9	8	4	1	..	35
80-89	1	1	9	7	4	2	..	..	24
70-79	..	5	8	10	4	..	..	..	27
60-69	..	6	3	3	2	3	1	..	18
50-59	1	3	7	3	2	3	..	..	19
40-49	..	4	5	3	4	..	..	1	17
30-39	.	2	3	2	2	4	..	..	13
20-29	..	..	4	4	3	..	..	..	11
10-19	..	1	3	7	2	2	1	..	16
0-9	..	..	2	5	8	5	1	..	21
Total	3	43	67	68	50	32	6	1	270
Mean		82.2	76.3	68.8	65.3	66.7			
Probable error of mean		3.17	3.04	3.04	3.79	5.16			
Standard deviation		29.6	36.9	37.2	39.8	41.8			
Coefficient of variability		36.0	48.4	54.1	60.9	62.7			
Mean of 224 cases with free acid		85.5	82.1	73.2	78.7	83.0			

In order to determine whether there is a true decline of gastric function with advancing years, it is necessary to know the total amount of acid secreted in each age period. This value is obtained by multiplying the mean volume by the mean total acidity for each decade. If,

then, the value in the age period from 20 to 29 is taken as 100 per cent. it is possible to estimate the percentage decline of gastric secretion in other age periods. This is shown in chart 3, and it is seen that there

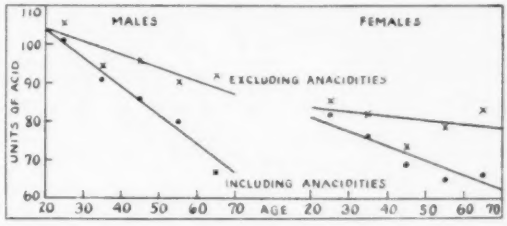

Chart 1.—Standards of normal. Relation of total acidity to age in various decades.

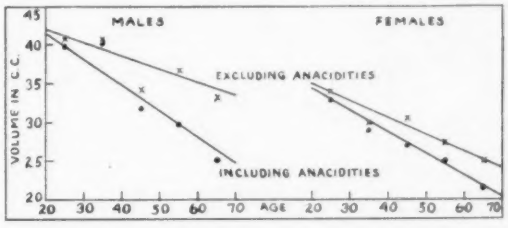

Chart 2.—Standards of normal. Relation of volume to age in various decades.

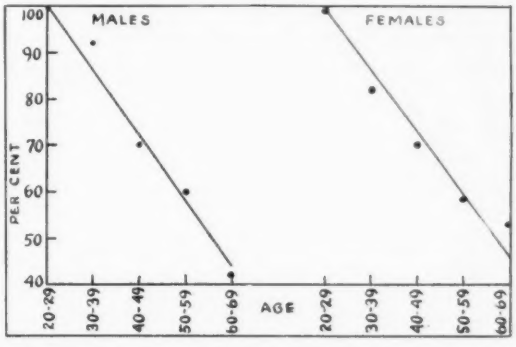

Chart 3.—Percentage decrease in total gastric secretion (volume times acidity) with advancing years (normal persons).

is a similar decrease in the total amount of secretion in both sexes. The importance of measuring the volume of secretion is clearly brought out, because if acidity alone is considered, it would appear that secretion decreased with age only in male subjects.

TABLE 4.—*Volumes of Secretion in Relation to Age and Sex (Normal Persons)*

Males

Volume, Cc.	Age, Years								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
90-94	..	1	..	..	..	..	..	..	1
85-89	..	..	..	..	..	..	..	..	..
80-84	..	..	..	..	..	..	..	..	..
75-79	..	1	2	1	2	..	..	..	6
70-74	1	1	2	2	..	..	..	..	6
65-69	1	..	4	1	..	..	..	..	6
60-64	..	5	5	2	3	..	..	..	15
55-59	..	..	3	1	2	..	..	..	6
50-54	..	7	7	8	..	4	..	..	26
45-49	..	4	3	8	5	3	..	..	23
40-44	..	19	17	8	8	3	..	..	55
35-39	3	6	5	11	2	2	1	1	31
30-34	..	9	15	20	4	3	1	..	52
25-29	1	8	12	15	6	1	2	..	45
20-24	1	5	2	10	11	3	2	..	34
15-19	..	2	2	7	7	3	2	..	23
10-14	..	..	4	5	6	4	3	..	22
5-9	..	1	3	6	5	3	..	..	18
0-4	..	1	..	2	4	6	1	1	15
Total	7	70	86	107	65	35	12	2	384
Mean		39.7	40.6	32.7	29.9	24.9			
Probable error of mean		1.21	1.21	1.01	1.51	1.99			
Standard deviation		15.1	16.7	15.6	18.0	17.5			
Coefficient of variability		38.0	41.1	45.8	60.0	70.0			
Mean of 326 cases with free acid		40.7	40.7	34.2	36.8	33.2			

Females

Volume, Cc.	Age, Years								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Total
90-94	..	..	..	..	..	..	..	..	..
85-89	..	..	..	..	..	..	..	..	..
80-84	..	..	..	..	..	..	..	..	..
75-79	..	..	1	..	..	..	..	..	1
70-74	..	..	1	..	..	..	..	..	1
65-69	..	..	..	..	..	..	..	..	..
60-64	..	3	..	2	1	..	..	..	6
55-59	1	..	..	..	1	..	..	..	2
50-54	1	1	2	2	3	1	..	..	10
45-49	..	4	3	4	1	..	..	..	12
40-44	..	3	5	5	1	2	..	..	16
35-39	1	7	7	3	2	1	1	..	22
30-34	..	7	14	10	9	6	..	..	46
25-29	..	6	4	9	6	3	2	..	30
20-24	..	5	16	9	7	4	..	..	41
15-19	..	6	6	6	6	2	1	..	27
10-14	..	1	4	4	6	8	1	1	25
5-9	..	..	4	11	5	4	..	..	24
0-4	..	..	..	3	2	1	1	..	7
Total	3	43	67	68	50	32	6	1	270
Mean		33.1	29.1	27.4	25.1	21.7			
Probable error of mean		1.29	1.11	0.97	1.36	1.45			
Standard deviation		12.6	13.5	11.8	14.3	12.2			
Coefficient of variability		38.1	46.4	43.1	57.0	56.2			
Mean of 224 cases with free acid		34.0	30.0	30.5	27.6	25.4			

UNEXPLAINED ANACIDITY

With the introduction of histamine as a stimulus of gastric secretion, it has become necessary to revise preexisting ideas about gastric anacidity. Many people who apparently secrete no free acid with other stimuli, give a normal, or nearly normal, response with histamine, and it is evident that the ordinary test meal is not adequate for determining whether or not the stomach is capable of secreting acid.

It is generally agreed that the incidence of anacidity increases with age. The best study of this problem has been made by Vanzant,[5] and further references to the literature are given in her paper. She studied cases in which free acid did not appear on repeated fractional analysis with the Ewald meal or (in a few cases) after the injection of histamine, and found that from youth to old age there was a straight line correlation between the incidence of anacidity and age, and that at all ages women showed a greater incidence of anacidity than did men. Recently Bockus, Bank and Willard,[6] using the histamine method, found the general incidence of anacidity much lower in a group of patients with gastro-intestinal complaints than in normal patients. Otherwise, their findings were in agreement with Vanzant's.

In the present series of 988 cases, there were 91 instances of unexplained anacidity, 9.3 per cent. The frequency in the male subjects was 7.3 per cent, and in the female subjects, 12.4 per cent. Exclusive of cases of carcinoma of the stomach and of pernicious anemia, there was an incidence of 10.8 per cent; 8.8 per cent for the male subjects and 13.3 per cent for the female subjects.

Of the 91 cases of anacidity, 12 showed evidence of a coexisting gastro-intestinal or debilitating disease, which, on the basis of the criteria laid down for normal people, necessitated their elimination from this study. There remained, then, 79 people who, except for the absence of acid, were entirely normal. Repeated checks with histamine in many of these cases showed that the condition was constant, and I have never seen an instance of anacidity after the administration of histamine in which there was a later return of free acid.

Table 5 shows frequency of anacidity among normal people at all ages. The figures are in close agreement with those of Vanzant,[5] and they show that there is a definite increase as people grow older, and that at all age periods, except beyond 60, there is a higher incidence in women than in men.

PEPTIC ULCER

The general implication of the literature is to the effect that there are no constant or characteristic findings on gastric analysis in cases

6. Bockus, H. L.; Bank, J., and Willard, J. H.: Achlorhydria with a Review of 210 Cases in Patients with Gastrointestinal Complaints, Am. J. M. Sc. **184**:185, 1932.

of peptic ulcer. However, Hurst [7] was impressed by the occurrence of duodenal ulcer in people who already had "hyperacidity," and while, in 53 cases of gastric ulcer, he found [8] 58.4 per cent with "hyperacidity," 32.1 per cent with "normal acidity" and only 9.5 per cent with "hypoacidity," no less than 90 per cent of 114 patients with duodenal ulcer had "hyperacidity" and 10 per cent had normal acidity. Brown [9] has summarized the question as follows: "Somewhat less than 50 per cent of patients show high normal or hyperacid conditions. Rather more than 50 per cent of cases are well within normal limits; occasionally subacidity occurs, and rarely anacidity." Cheney and Bloomfield,[10] using a special alcohol test meal, observed that in all but 1 of 37 cases of peptic ulcer the gastric acidity and volumes of secretion were greater than normal. Comfort and Osterberg,[11] using the histamine test in 40 cases of duodenal ulcer, found a range of from 30 to 135 units of acid, and in 11 cases of gastric ulcer, a range of from 25 to 95 units of acid.

Table 5 shows frequency of anacidity among the normal people at all

Age, Years	Males			Females		
	Total Cases	Anacidity Cases	Percentage	Total Cases	Anacidity Cases	Percentage
10-19	7	0	0.0	3	0	0.0
20-29	70	2	2.9	43	2	4.7
30-39	86	3	3.5	67	5	7.5
40-49	107	12	10.0	68	13	19.1
50-59	65	9	13.9	50	9	18.0
60-69	35	11	31.7	32	7	21.9
70+	14	4	28.6	7	2	28.6
Total	384	41	10.7	270	38	14.1

They stated that the volumes in these cases were too variable to be of significance, but their technic is open to criticism.

In the present series there were 130 cases of duodenal ulcer, 112 in male and 18 in female patients, and 36 cases of gastric ulcer, 31 in male and 5 in female patients. In order to avoid questionable cases, the diagnosis was based on unequivocal roentgen evidence. In some instances there was surgical confirmation.

Acidity.—The heavy line in chart 4 shows the mean total acidity at various age periods in normal people. Each dot indicates the highest total

7. Hurst, A. F.: Hypersthenic Gastric Diathesis and the Pathology, Prophylaxis and Treatment of Duodenal Ulcer, Lancet **2**:1369, 1922.

8. Hurst, A. F., and Venables, J. F.: The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, Guy's Hosp. Rep. **9**:249, 1929.

9. Brown, T. R., in Cecil, R. L., and Kennedy, Foster: A Text-Book of Medicine, Philadelphia, W. B. Saunders Company, 1927, p. 655.

10. Cheney, G., and Bloomfield, A. L.: Gastric Function in Cases of Gastric and Duodenal Ulcer, J. Clin. Investigation **5**:511, 1928.

11. Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine, J. A. M. A. **97**:1141 (Oct. 17) 1931.

acidity in a single case of gastric ulcer and each x represents a single case of duodenal ulcer.

That the acidity in practically every instance is above the mean is strikingly shown. There is 1 case of gastric ulcer among the male subjects in which it is below 50, and 1 case of duodenal ulcer among the female subjects in which it is below 60. Ninety-one and three-tenths per cent of all the cases of duodenal ulcer and 91.7 per cent of all the cases of gastric ulcer are above the mean line. The broken line shows the mean acidity of all the cases of ulcer. It is apparent, as in normal people,

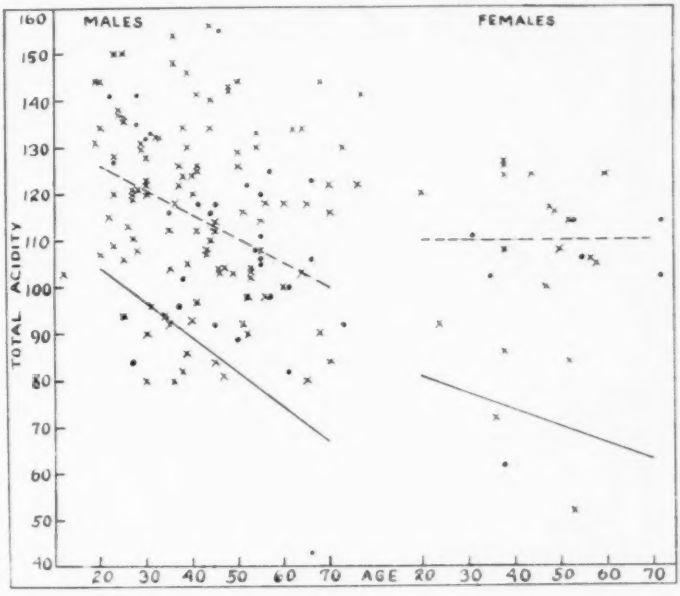

Chart 4.—Total acidity in peptic ulcer. Relation to normal mean.

that the mean acidity of the cases of ulcer in male patients falls with advancing years. The number of female subjects is too small to be significant, but the mean acidity was about the same at all age periods.

Volume.—In chart 5, each dot represents the maximum ten-minute volume of secretion in a single case of gastric ulcer, and each x represents the volume in a case of duodenal ulcer. Again, one sees that the majority of cases are above the mean line. However, there is more scattering than with the acid values, and the highest volumes are in the duodenal ulcer group. There were only 8 patients in whom the volume was as low as 20 cc. or less; 79.2 per cent of the cases of duodenal ulcer and 75 per cent of the cases of gastric ulcer are above the mean

line. The broken line represents the mean value for the cases of ulcer in male patients, and shows a definite fall with advancing years. The mean value for the female patients could not be estimated, because there were too few cases.

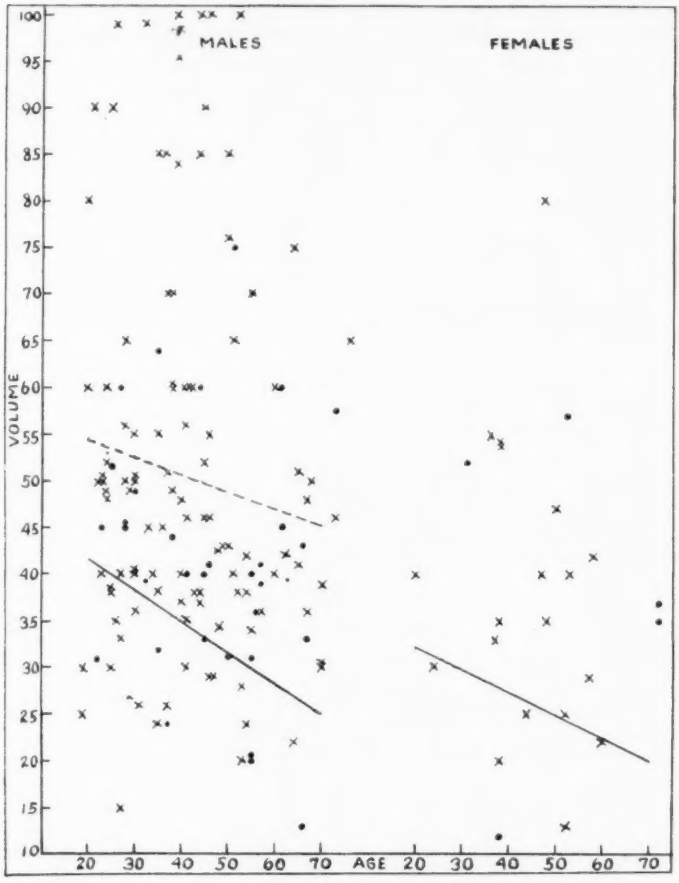

Chart 5.—Volume of secretion in peptic ulcer. Relation to normal mean.

CARCINOMA OF STOMACH

One cannot here discuss the voluminous literature on gastric secretion in carcinoma of the stomach, and the reader is referred to the paper of Polland and Bloomfield.[12] However, most observers agree

12. Polland, W. S., and Bloomfield, A. L.: Gastric Secretion in Cancer of the Stomach, Bull. Johns Hopkins Hosp. **46**:307, 1930.

as to the frequency of anacidity in this disease, although they find acid present—usually diminished—in a certain percentage of cases. Practically all the reported work has been done with gastric contents removed after a test meal of some sort. High acid values have been found by very few workers in verified instances of carcinoma. The only data available on the important question of volume of secretion and on acid values after a powerful stimulus such as histamine are those of Polland and Bloomfield,[12] who found, in 19 carefully studied cases, that there were usually small volumes of secretion with low acidity, or with an absence of acid.

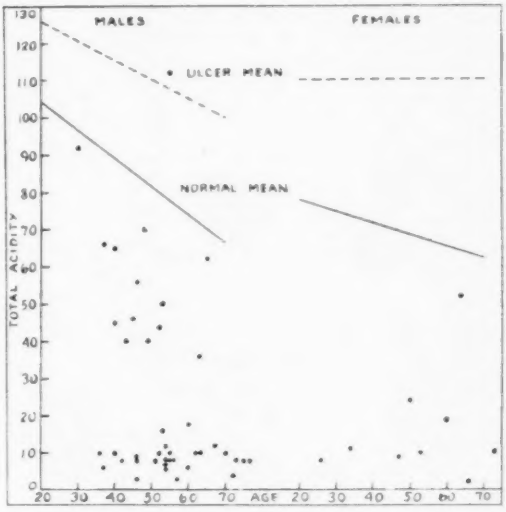

Chart 6.—Total acidity in carcinoma of stomach. Relation to normal mean and to ulcer mean.

In the present series, there were 56 cases of carcinoma of the stomach; 46 in male and 10 in female patients. The diagnosis in nearly every case was verified by operation or at autopsy.

The only variation from the usual technic was that if pyloric obstruction existed, the stomach was carefully washed out before the analysis was made. This was done to avoid dealing with a mixture of foreign materials, which gives no idea of what sort of gastric juice, if any, the stomach is actually secreting.

Acidity.—In striking contrast to the ulcer group, the majority of these patients had no acid or a low acid value. The incidence of anacidity was 69.6 per cent. In chart 6 it is seen that only 7 of the cases yielded values approaching normal, and of these, there was only 1 above

normal. In this chart, the ulcer mean, as well as the normal, is given, and the relation between the type of secretion in cancer and in ulcer cases is brought out more strikingly.

Volume.—One of the most striking features of the gastric secretion in these cases is the small volume. In the patients with anacidity, the maximum amount obtained was seldom over 10 cc., and the material was mostly mucus. In the cases in which acid was obtained, the amount of juice was usually small. In chart 7, the highest ten minute yield from all patients with carcinoma of the stomach is plotted in relation to the mean normal and mean ulcer values at various age periods.

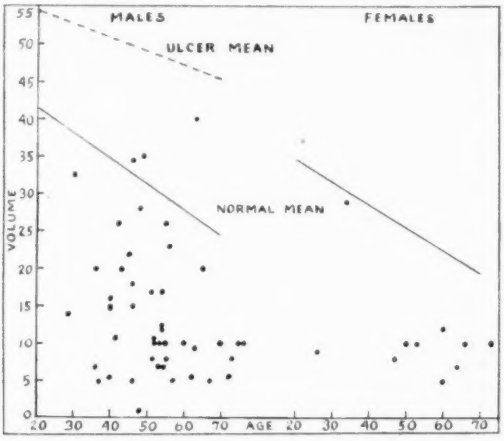

Chart 7.—Volume of secretion in carcinoma of stomach. Relation to normal mean and to ulcer mean.

From this it can be seen that only 9 cases approach the normal, and of these, only 3 are above normal.

DIAGNOSTIC VALUE OF HISTAMINE TEST MEAL IN DIFFERENTIATING BENIGN FROM MALIGNANT CONDITIONS OF STOMACH

One of the main objects of this study was to set standards by which findings in gastric disorders could properly be compared. Are there, for example, in cancer or in ulcer, secretory findings which deviate in such a way that practical conclusions can be drawn? A glance at tables 3 and 4 (normal persons) shows that no exclusive findings are likely to be obtained in disease, and the matter resolves itself into a question of frequencies. A study of charts 4, 5, 6 and 7 shows that benign and malignant diseases of the stomach yield entirely different types of gastric response to histamine. Although there is some overlapping of the

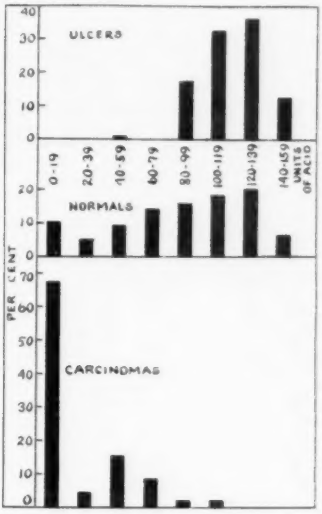

Chart 8.—Frequency distribution of total acidity in normal males and in cases of carcinoma and of ulcer.

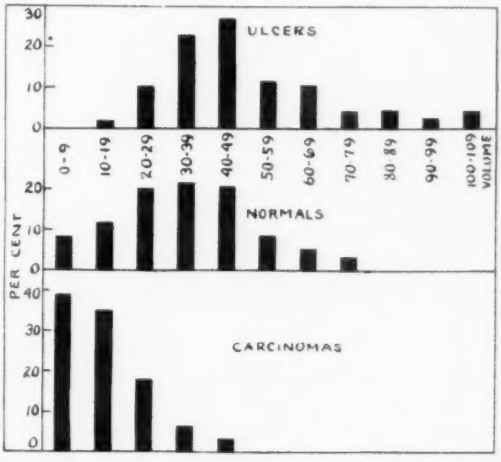

Chart 9.—Frequency distribution of volume in normal males and in cases of carcinoma and of ulcer.

values, particularly the volumes, the vast majority of patients with ulcer fall within the high acid, high volume range, whereas the vast majority of cases of carcinoma fall within the low acid, low volume range. To emphasize this point further, a frequency distribution of the values of total acidity in normal people and in the ulcer and cancer cases (male subjects) is shown in chart 8, and a similar graph of the volumes

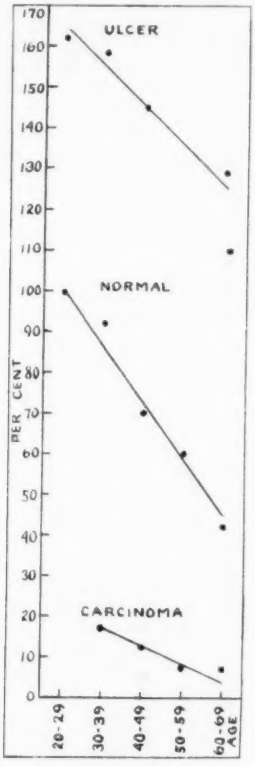

Chart 10.—Percentage of total gastric secretion with ulcer and with carcinoma (males).

appears in chart 9. Although one cannot say, from the secretion, with absolute certainty that a particular lesion is benign or malignant, it seems that the original assumption of Bloomfield and Polland [1] is correct, and that the histamine test meal, as advocated by them, may be of great value as a diagnostic procedure in doubtful cases of pyloric lesion.

In order to emphasize further the value of knowing the total gastric secretion (volume acid) rather than just the concentration of acid alone,

chart 10 has been constructed so that the mean total amount and acid secreted at each age period in the cases of ulcer and of carcinoma in male patients can be compared. The value in the age period from 20 to 29 of the normal male subjects is taken as 100 per cent. When this is done, it is found that cases of ulcer which have a relatively low acid often have a high volume, so that the total secretion falls in the high range, whereas cases of carcinoma almost invariably have a low total secretion. Eighty-seven and one-tenth per cent of male patients with gastric ulcer and 92.5 per cent of the male patients with duodenal ulcer had total secretions above, while 100 per cent of the male patients with carcinomas had total secretions below the normal mean for age.

MISCELLANEOUS DATA

There were 30 cases of pernicious anemia which showed complete anacidity. In 22 cases of verified disease of the gallbladder, the range of acidity and of volume was so wide that no diagnostic conclusions could be drawn, a finding not in harmony with the claim so often made that disease of the biliary tract is associated with subnormal gastric secretion. None of the other groups of cases was large enough to analyze.

COMMENT

The present study is the first to be based on a large series (nearly 1,000) of standard histamine tests carefully executed by a trained personnel. The results, therefore, should be definitive, and it is hoped that the question of normal standards, as well as the findings in certain disorders, are now settled for all time. Furthermore, these are the only extensive observations on the volume of gastric secretion in man, a matter of prime importance from both the physiologic and the chemical standpoint,[13] as the facts that have been presented clearly show. It is not the present purpose to debate the relative merits of various tests of gastric function, as the question has recently been fully discussed from this clinic.[14] Discussion, furthermore, seems pointless since many of the recent papers represent not a critical examination of the facts, but special pleading by men who are obviously biased by reason of sentiment or tradition in favor of one or another of the older procedures. I shall dismiss the question, then, by reiterating that the histamine test is the only available procedure which fulfils the recognized criteria of an adequate functional test; it is standardizable; it imposes a maximum load on function, and it yields pure juice suitable for quantitative measurement.

13. Bloomfield, A. L., and Keefer, C. S.: Gastric Motility and the Volume of Gastric Secretion in Man, J. Clin. Investigation **5**:295, 1928; footnote 4.

14. Bloomfield, A. L.: Clinical Aspects of Gastric Secretion, Ann. Int. Med. **6**:307, 1932.

With regard to normal standards, the previous observations of Polland and Bloomfield, Vanzant and Alvarez and others are confirmed and extended. The outstanding fact is that there is no narrow zone into which the secretions of all healthy people fall; acid values from 0 to 160 and ten minute volumes of from 10 to 100 cc. are encountered. There is, to be sure, a peak to the distribution curves, but it seems clear that hypo-acidity and hyperacidity as pathologic clinical states must be abandoned. The differences between the sexes and the fall in the rate of secretion with advancing years, especially in male subjects, are phenomena of physiologic interest and also of great clinical importance, since they clearly must be taken into account in assessing gastric function in disease.

Since the normal range is so great, it becomes clear that only when the case is extreme can information of consistent diagnostic value be obtained from measurements of gastric secretion; in peptic ulcer, cancer of the stomach and pernicious anemia, such is the case, but fruitful application of these studies is obviously limited in clinical practice, and further minor modifications of technic are not likely to be of much more help.

SUMMARY

An analysis has been made of 988 consecutive histamine test meals. Six hundred and eighty-four of the patients showed no evidence of disease, and standards of normal for gastric acidity and volume of secretion were derived from these data.

The mean total acidity for male subjects ranged from 101.1 units at the age of 25 to 67.1 units at the age of 65. The mean total acidity for female subjects ranged from 82.2 units at the age of 25 to 66.7 units at the age of 65. This included normal subjects who had anacidity. In the case of the male subjects, there was a definite correlation between age and acidity.

The mean maximum ten minute volume of secretion for male subjects ranged from 39.7 cc. at the age of 25 to 24.9 cc. at the age of 65. The mean volume of secretion for the female subjects ranged from 33.1 cc. at the age of 25 to 21.7 cc. at the age of 65. There was a definite correlation between age and volume in the two sexes.

In both sexes the total gastric secretion declined with age at about the same rate.

There was a steady increase in the incidence of anacidity from youth to old age, and at all age periods up to 60 the incidence was higher in female than in male subjects. The incidence for the normal male subjects was 10.7, and for the normal female subjects, 14.1 per cent.

In 130 cases of duodenal ulcer, 91.3 per cent of the subjects had a total acidity and 79.2 per cent had volumes of secretion higher than the mean values of normal persons of the same age and sex.

In 36 cases of gastric ulcer, 91.7 per cent of the patients had a total acidity and 75 per cent had volumes of secretion higher than the mean values of normal people of the same age and sex.

In 56 cases of carcinoma of the stomach, the incidence of anacidity was 69.6 per cent. In the 56 cases, there was only 1 patient who had an acidity and 3 who had volumes above the mean normal value for the same age and sex.

Eighty-seven and one-tenth per cent of male patients with gastric ulcer and 92.5 per cent of male patients with duodenal ulcer had total secretions above the normal mean for age, and 100 per cent of male patients with carcinomas had total secretions below this mean.

The diagnostic value of the histamine test meal in differentiating benign from malignant lesions of the stomach is discussed.

In a miscellaneous group of cases, no evidence could be found that any particular disease, except pernicious anemia, was associated with a characteristic type of gastric secretion.

PEPTIC ULCER

VIII. RESULTS OF MEDICAL AND SURGICAL TREATMENT OF PATIENTS IN RURAL DISTRICTS AND IN SMALL TOWNS

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During recent years many statistical studies of peptic ulcer have appeared in the literature. Most of them have dealt with patients in the larger cities. At the University of Virginia Hospital, however, the majority of the patients come from rural districts and the smaller towns and cities. Many of the patients present peculiar problems because of their economic and social status, their mode of living and their dietary habits and limitations. Mountaineers, farmers cultivating poor soil and others unaccustomed and often unable to procure any but the roughest sort of diet tax the ingenuity of the internist who would treat them medically for peptic ulcer.

In this study an attempt has been made to evaluate the late results of the medical and surgical treatment of all patients with peptic ulcer seen in the hospital during a ten year period, 1918 to 1928. For the purpose of comparison, a brief summary of the literature of statistical and follow-up studies precedes the presentation of the data.

MEDICAL STATISTICS

Of especial interest is the recent report made by Brown,[1] an associate of the late Dr. Sippy. He surveyed all their cases in the Presbyterian Hospital, Chicago, from 1912 to 1928 and also included 167 cases of former associates. Cases with an inconclusive diagnosis were excluded. Questionnaires were sent to 1,900 patients, and 1,224 cases thus followed were studied carefully. Of this number, 917 (75 per cent) were in men and 307 (25 per cent) in women. The average age at which symptoms commenced was 35 years. The average time between the onset of symptoms and the first examination was seven and one-half years. The patients complained of actual pain in 51 per cent of cases and of discomfort in 49 per cent, both usually sharply localized in the epigastrium. Spontaneous vomiting occurred in 17 per cent of the

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From the University of Virginia.

1. Brown, R. C.: The Results of Medical Treatment of Peptic Ulcer, J. A. M. A. **95**:1144 (Oct. 18) 1930.

cases and hemorrhage, either prior to or after treatment, in 24 per cent. Perforation occurred in 4 per cent.

Of the 1,224 patients successfully followed, 1,130 had been treated medically and 94 (7.7 per cent) surgically. No report was made of the latter group, but of those treated medically, 49.5 per cent were graded as cured, 16.7 per cent as satisfactorily improved and about 10 per cent as moderately improved; in 20 per cent there had been a failure to obtain relief by medical measures.

Brown conceded that the "cured" patient might have a recurrence of symptoms at any later time. He noted that the early cases offered the best chance for a cure. In the cases seen later, scarring at the site of ulceration was common, obstruction to the outlet of the stomach not infrequent and the results of medical treatment, therefore, often unsatisfactory. Obstruction due solely to acute inflammatory tissue was usually relieved by treatment in two or three weeks. Failure to respond denoted scarring, which he said should be an indication for surgical intervention. He concluded that in addition to the 7.7 per cent of patients who were treated surgically, the 20 per cent of patients in whom medical treatment had failed should have received surgical treatment. In his opinion the most serious problem to be faced is the inability of physicians to insure an individual with peptic ulcer against recurrence.

While the most carefully controlled treatment initiated by rest in bed is prescribed by the Sippy regimen, many clinicians now feel that most patients with peptic ulcer respond almost as well to a less rigorous and ambulatory treatment. Blackford and Bowers [2] of Seattle studied two similar groups of patients, one hospitalized, the other ambulatory, and found almost equally good results, about 60 per cent satisfactory improvement, in both groups.

Lynch,[3] in analyzing 944 cases of peptic ulceration at the Montreal General Hospital, found that the incidence of peptic ulcer was 1.45 per cent of the total hospital admissions. He stated that 72 per cent of the patients had been treated medically and 28 per cent surgically. Of those treated medically, 153 gastric and 165 duodenal ulcers had been treated by the Lenhartz regimen, with 65 per cent and 78 per cent satisfactory results, respectively, while 57 gastric and 137 duodenal ulcerations had been treated by the Sippy method, with 60 per cent and 81 per cent satisfactory results, respectively. In the cases in which hemorrhage was a complication he advised operative treatment as soon

2. Blackford, J. M., and Bowers, J. M.: A Comparison of the Late Results of Ambulatory and Hospital Treatment of Peptic Ulcer, Am. J. M. Sc. **177**:51, 1929.

3. Lynch, R.: Analysis of Ulcer of the Stomach and Duodenum, Canad. M. A. J. **17**:677, 1927.

as the patient could be adequately rehabilitated, usually within a period of from four to five weeks.

Miller, Prendergrass and Andrews,[4] of Philadelphia, reported results very similar to those previously quoted. They noted that while the acidity of aspirated gastric chyme tended to be high in patients with peptic ulcer, nevertheless many apparently normal persons had an equally high gastric acidity. This is in accord with similar results previously published by me.[5]

Eusterman,[6] in discussing Brown's study, mentioned Nielson, Crohn, Greenough and Joslin as averaging about 27 per cent "cures" in their cases of medically managed peptic ulcer. He said that of 520 patients treated medically at the Mayo Clinic, 35 per cent considered themselves cured. An additional 43 per cent were definitely improved and lost no time from work.

Many have recognized that while the medical management of ulcerations may present striking immediate results, the later results are less encouraging. Einhorn and Crohn [7] in a follow-up study of 100 patients one year after treatment classified 67 per cent as cured and 22 per cent as much improved. After four years, however, only 27 per cent could be included as cured, while 23 per cent were improved.

Short,[8] in a comprehensive review of the statistical literature of peptic ulcer from England, America and several European countries, made the following summary:

> Given the best medical treatment three out of four cases of gastric or duodenal ulcer, probably more, will become symptom free. Only 40 per cent of these patients will remain well and from 15 to 19 per cent will be dead in about 10 years. Early cases do well, long-standing cases badly.

SURGICAL STATISTICS

In 1930, the American Surgical Association conducted a symposium on the surgical treatment of peptic ulcer. Many interesting and important facts were elicited and opinions crystallized. St. John,[9] in report-

4. Miller, T. G.; Prendergrass, E. P., and Andrews, K. S.: A Statistical Study of Clinical and Laboratory Findings in Gastric and Duodenal Ulcer, with Special Reference to Roentgenologic Data, Am. J. M. Sc. **177**:15, 1929.

5. Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, Am. J. M. Sc. **177**:65, 1929.

6. Eusterman, G. B.: Discussion of Brown.[1]

7. Einhorn, M., and Crohn, B. B.: Follow-Up of One Hundred Cases of Gastroduodenal Ulcer Treated by Medical Means, Am. J. M. Sc. **172**:691, 1926.

8. Short, A. R.: The Treatment of Gastric and Duodenal Ulcer: A Statistical Inquiry, Brit. M. J. **1**:435, 1931.

9. St. John, F. B.: A Follow-Up Study of the Results in Surgical Therapy for Gastric and Duodenal Ulcer, Ann. Surg. **92**:597, 1930.

ing the results at the Presbyterian Hospital, New York City, called attention to the fact that: "It must be borne in mind in comparing surgical and medical results that surgery in most clinics today in simple ulcer is only instituted at the point where medicine has failed."

Balfour [10] reported from the Mayo Clinic the results of gastroenterostomy in 500 cases of duodenal ulcer and 100 cases of gastric ulcer followed for a period of from five to ten years. In the patients with duodenal ulcer males outnumbered females five to one. There was an operative mortality of only 1.8 per cent, with 4.28 per cent of deaths within five years. The follow-up revealed satisfactory relief from symptoms in 87 per cent of cases. There was complete relief in 69 per cent, fair relief in 18 per cent and failure in 13 per cent of the cases. Recurrent ulceration was encountered in 4.07 per cent of 491 patients, including the occurrence of gastrojejunal ulcer in 3.26 per cent (16 cases), incidentally only about one-half the mortality rate following gastrectomy.

In the patients with gastric ulcer the operative mortality was 3 per cent, with 17 per cent of deaths within five years. The follow-up revealed satisfactory results in 79 per cent of the cases. There was complete relief from symptoms in 50 per cent, fair relief in 4 per cent and poor results in 17 per cent of the cases. Carcinoma was discovered later in 6 of the patients.

In a previous paper by Balfour [11] giving his results of gastroenterostomy in 100 physicians, the operative mortality was 1.82 per cent in the duodenal and 4.7 per cent in the gastric group. Eight and one half years after operation the result was satisfactory in 93 per cent of the patients.

Judd and Hazeltine [12] reported from the Mayo Clinic the results of operations for excision of ulcer of the duodenum including excision of part of the pyloric ring. Of 464 patients operated on from 1924 to 1928, 369 were traced. The operative mortality was only 0.43 per cent. The results were satisfactory in 90 per cent of the cases, and in only 8.1 per cent was there no benefit. Deaver and Burden [13] also advocated operation on the pyloric ring in the surgical treatment of duodenal ulceration.

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10. Balfour, D. C.: Results of Gastroenterostomy for Ulcer of the Duodenum and Stomach, Ann. Surg. **92**:558, 1930.

11. Balfour, D. C.: The Results of Operation for Duodenal Ulcer in Physicians, Ann. Surg. **86**:691, 1927.

12. Judd, E. S., and Hazeltine, M. E.: The Results of Operations for Excision of Ulcer of the Duodenum, Ann. Surg. **92**:563, 1930.

13. Deaver, J. B., and Burden, V. G.: Further Experience with Resection of the Anterior Half of the Pyloric Sphincter, Ann. Surg. **92**:533, 1930.

Gatewood [14] from the Presbyterian Hospital, Chicago, reported 163 cases of peptic ulcer in which the patients were treated surgically, with an operative mortality of 1.8 per cent. Of this group, 82 per cent were either entirely well or greatly improved, 8.5 per cent died subsequently of gastric disease, while 4.8 per cent died of other causes.

Horsley,[15] from Richmond, reported 160 cases in which the patients were treated by various operations. His total operative mortality was 6 per cent, and 59 per cent of the patients were either symptom-free or greatly improved after operation.

Argument concerning the rôle of gastrectomy in the treatment of duodenal ulceration has been frequent since Lewishorn's [16] statistics from the Mount Sinai Hospital, New York, revealed the occurrence of gastrojejunal ulcer in 34 per cent of their patients who had been treated by gastro-enterostomy and Berg [17] published his results of partial gastrectomy. Berg's operative mortality was 6.9 per cent and a gastrojejunal ulceration occurred in only 1.1 per cent of the cases. With these exceptions the results were practically 100 per cent satisfactory.

Finney and Hanrahan [18] reported the cases in which surgical treatment was given at the Johns Hopkins Hospital; there were a general operative mortality of 8.6 per cent and 84.6 per cent of satisfactory results.

In discussing gastro-enterostomy, Balfour [19] said:

> When the American Surgical Association presents such figures as these from various members and they all run between 85 and 90 per cent (good results) it is convincing evidence of what can be accomplished in chronic duodenal ulcer by indirect operation alone.

PEPTIC ULCER AT THE UNIVERSITY OF VIRGINIA HOSPITAL

Incidence.—During the ten year period, from 1918 to 1928, the total combined admissions to the medical and surgical services numbered 32,938. In that number of patients the diagnosis of peptic ulcer of the stomach or duodenum was recorded in 370 instances, an incidence of 1.12 per cent (table 1).

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14. Gatewood: The Immediate Mortality and Late Results of Operations for Peptic Ulcer, Ann. Surg. **92**:554, 1930.

15. Horsley, J. S.: The Immediate Mortality and Late Results of Operations for Gastric and Duodenal Ulcers, Ann. Surg. **92**:545, 1930.

16. Lewishorn, R.: The Frequency of Gastrojejunal Ulcers, Surg., Gynec. & Obst. **40**:70, 1925.

17. Berg, A. A.: The Mortality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer, Ann. Surg. **92**:340, 1930.

18. Finney, J. M. T., and Hanrahan, E. M., Jr.: Results of Operations for Chronic Gastric and Duodenal Ulceration, Ann. Surg. **92**:620, 1930.

19. Balfour, D. C.: Ann. Surg. **92**:638, 1930.

Among the 370 patients admitted there were 286 with ulcer of whom 220 had duodenal and 66 gastric ulceration. Two were suspected of having both gastric and duodenal ulceration. There were 247 patients of the white and 39 of the Negro race. Comparing these figures with the total number of white and Negro patients admitted to the hospital, there was almost twice as high an incidence of peptic ulcer in the white as in the Negro race. There were 219 males and 67 females. The most frequent age incidence was the decade between 30 and 40 years. The patients were almost equally divided as to town and rural residence, with a slight preponderance of those living in strictly rural districts. In more than half of the patients the symptoms had been present for more than two years.

Complications.—Of the complications, hemorrhage was the most frequent, occurring as gross blood in the vomitus or stools in 68 cases

TABLE 1.—*Incidence of Cases of Peptic Ulcer at University of Virginia Hospital*

	Hospital Admissions			Peptic Ulcer Admissions		
Year	Medical	Surgical	Total	Medical	Surgical	Total
1918	1,600	1,715	3,315	23	9	32
1919	1,120	1,921	3,041	16	8	24
1920	1,084	1,947	3,031	9	6	15
1921	1,230	2,245	3,475	16	5	21
1922	1,438	2,196	3,634	25	13	38
1923	1,594	2,372	3,966	21	15	36
1924	1,390	2,203	3,593	45	21	66
1925	1,549	1,461	3,010	29	16	45
1926	1,450	1,314	2,764	37	9	46
1927	1,594	1,515	3,100	38	9	47
Totals	14,049	18,889	32,933	259	111	370

or almost one fourth of the patients. Obstruction and perforation were much less frequent.

Treatment.—Medical treatment was employed in 196 (68.6 per cent) of the cases and surgical treatment in 90 (31.4 per cent). Operation was advised for 16 (5.5 per cent) additional patients, but they preferred medical management. Except in cases in which there was marked obstruction at the pylorus, in some cases of hemorrhage and in all of those with perforation of the ulcer, medical treatment was given a trial before operation was advised.

Of the deaths in the hospital, 6 occurred during medical treatment and 8 among the 90 patients treated surgically, including the 24 with perforated ulcers (table 2).

Results.—Of the 272 patients discharged from the hospital 190 had been treated medically and 82 surgically. Follow-up letters were sent to each of them. In some instances the patients reported on their condition by a personal interview, in some long letters in addition to the completed questionnaire were forwarded, and in others merely the com-

TABLE 2.—*Comparative Data for Patients with Gastric and Duodenal Ulcers*

		Site of Ulceration			
		Gastric	Duodenal	Totals	
Number		66	220	286	
Race	White	57	190	247	
	Negro	9	30	39	
Sex	Male	42	177	219	
	Female	24	43	67	
Age (years)	1–20	4	10	14	
	21–30	13	50	63	
	31–40	16	67	83	
	41–50	13	47	60	
	51 plus	20	46	66	
Residence	City or town	33	104	137	
	Country	33	116	149	
Duration of symptoms	1 month or less	12	13	25	
	1 to 6 months	10	25	35	
	6 months to 1 year	4	22	26	
	1 to 2 years	7	23	30	
	2 years or more	33	137	170	
Complications	Obstruction	4	33	37	
	Hemorrhage	19	49	68	129
	Perforation	9	15	24	
Treatment	Medical	43 (65%)	153 (69.6%)	196	
	Surgical	23 (35%)	67 (30.4%)	90	286
	Surgery refused	5	11	16	
Hospital result	Medical death	4	2	6	
	Surgical death	4	4	8	
	Discharged	58	214	272	
Follow-up	Letters sent	58	214	272	
	Replies	33	131	164	

TABLE 3.—*Comparison of the Results of Medical and Surgical Treatment*

			Method of Treatment			
			Medical		Surgical	
			Gastric	Duodenal	Gastric	Duodenal
Site of ulceration						
Number of patients followed-up (164)			25	85	8	46
Subsequent Deaths	Unqualified		3	2	0	2
	Not from ulcer		0	2	0	2
	From ulcer		0	2	0	0
	From carcinoma of stomach		3	0	0	0
	From probable carcinoma of stomach		0	0	1	0
Patients Still Living Jan. 1 1930	General result	Excellent	2	6	4	26
		Good	9	31	3	10
		Fair	6	28	0	3
		Poor	2	14	0	3
	Symptomatic result	No symptoms	5	17	4	24
		Occasional symptoms	13	48	3	14
		Frequent symptoms	1	14	0	4
	Economic result	Full time work	12	54	6	37
		Part time work	7	20	1	3
		Unable to work	0	5	0	2
	Dietary restriction	None	7	21	4	25
		Occasional food intolerance	5	13	2	11
		Necessary occasionally	4	13	1	3
		Necessary constantly	3	32	0	3
	Alkali required	None used	9	23	4	29
		Occasionally	9	36	3	10
		Frequently	1	20	0	3
	Subsequent operation necessary		0	6	0	0
	Subsequent gastrojejunal ulcer		0	0	0	3

pleted questionnaire was returned. Altogether 164 patients were followed, the time that had elapsed since treatment varying between twelve years and two years.

The results were recorded without knowledge at the time as to whether medical or surgical treatment had been employed. An effort was made to evaluate the symptomatic and economic results and to correlate this with the necessity of adhering to dietary restriction and the use of alkalis. All these factors were then estimated and the patient finally classified as having obtained excellent, good, fair or poor general results (table 3).

As subdivided into groups the number of cases in each is too small to reduce to accurate percentages. In order to express the figures, however, certain proportions may be stated. Of the medically treated, living patients, slightly more than one half with gastric ulceration and a few less than one half with duodenal ulceration obtained satisfactory results. In very few in either group, however, were the results classified as excellent. Of 25 patients with gastric ulcer 3 had died subsequently of known carcinoma of the stomach and 3 of unspecified causes. In 85 patients with duodenal ulcer 2 had died from the ulcer, 2 from other causes and 2 from unspecified causes. Subsequent operation had been performed in 6 of the patients.

Of the surgically treated living patients, all of those with gastric ulceration and more than three fourths of those with duodenal ulceration obtained satisfactory results. Half in the gastric and more than half in the duodenal group were classified as having obtained excellent results. Of 8 patients with gastric ulcer 1 had died subsequently of suspected carcinoma of the stomach. In 46 patients with duodenal ulcer, 2 had died from other causes than ulcer and 2 from unspecified causes. There were 3 patients in whom gastrojejunal ulceration apparently had developed.

Comparing the symptomatic results, there was definitely more complete relief from surgical than from medical treatment. The same was true of the economic results. As regards the necessity for dietary restriction and the use of alkalis, it was quite apparent that the majority of those treated medically had to adhere more or less strictly to dietary regulation and had to employ alkalis fairly regularly, while the majority of those treated surgically were able to eat more or less normally and seldom had to resort to the use of alkalis. Many of the patients treated medically had been readmitted to the hospital on two or more occasions for additional intensive treatment because of a persistence or recurrence of distressing symptoms. Several of them finally came to operation at the University of Virginia Hospital and have been included in these

statistics as surgically and not medically treated patients. As already mentioned, 6 of the patients followed and recorded as medically treated in this hospital reported such an unsatisfactory result that surgical treatment had been necessary and had been administered elsewhere.

COMMENT

The incidence of peptic ulceration among the patients of the University of Virginia Hospital was slightly lower than that given by Lynch of the Montreal General Hospital.

The larger number of admissions (370) than patients (286) is accounted for in the main by patients treated medically who returned during the ten year period for additional courses of intensive medical treatment or surgical intervention because of the persistence or recurrence of symptoms.

There were a little less than three and one-half times as many duodenal as gastric ulcers. This is considerably lower than the usually quoted four or five to one ratio. The most frequent incidence of the disease in the third decade of life is similar to that commonly observed. While the patients were practically equally divided as to town and country residence, it may be said that practically all the patients led a rather rural life, relatively few of them coming from truly urban communities.

The tabulations revealed that 31.4 per cent of all the patients with peptic ulcer had been treated surgically, while only 68.6 per cent had persisted with medical management. Further analysis revealed that 69.6 per cent of the patients with duodenal ulceration and 65 per cent of those with gastric ulceration had been treated medically, while 30.4 per cent of those with duodenal ulceration and only 35 per cent of those with gastric ulcer had been treated surgically. Balfour [20] stated that during 1931 at the Mayo Clinic 30 per cent of the inflammatory lesions of the duodenum were treated surgically. He did not state the percentage in gastric ulcer but said that:

> It is imperative, however, to realize that by no method of examination can the character of such lesions be positively identified. If, therefore, ulceration of the stomach does not show prompt response (roentgenologically) to medical treatment in ten days or two weeks, operation should be advised, and when efficiently carried out, it offers excellent prospect of permanent control of the disease.

Lahey [21] recently expressed a similar policy. The fact that 3 of 25 patients who were treated medically for gastric ulceration later died of

20. Balfour, D. C.: Annual Report of Operations on the Stomach and Duodenum for 1931, Proc. Staff Meet., Mayo Clin. **7**:99 (Feb. 17) 1932.

21. Lahey, F. H.: The Selection of Gastric Ulcers for Surgery, Surg., Gynec. & Obst. **54**:251 (Feb.) 1932.

known carcinoma of the stomach is a sufficient reminder of the importance of the ablation of all gastric ulcers that do not respond quickly and quantitatively, as demonstrated roentgenologically, to medical management. Many circumscribed carcinomatous gastric lesions masquerade as benign ulcer, and only by prompt surgical intervention will the appallingly high mortality of gastric carcinoma be lowered. To advise surgical removal of the ulcer for these patients is the duty and responsibility of both the internist and the surgeon.

That almost as many deaths occurred in the hospital while patients were under medical as under surgical treatment indicates that neither is devoid of risk. This fact is even more apparent when it is considered that in the 90 patients with peptic ulcer treated surgically perforation of the ulcer had occurred in 24 instances.

Analysis of the tabulations reveals that in the type of patient seen at the University of Virginia Hospital the results of surgical treatment are distinctly better than those of medical treatment. The economic and social status of many of these persons, their mode of living and their dietary habits and limitations may account in part for the fact.

To advise and outline a medical regimen that of necessity must contain some of the dietary niceties of life and the preparation of which presupposes certain further culinary proficiency is not difficult. However, it may often be practically impossible for persons economically and otherwise handicapped to adhere to this regimen.

In conclusion, this study leads me to believe that the management of peptic ulcer must be prescribed with due regard to the site of the lesion and the type of patient afflicted.

For patients with duodenal ulcer who are economically able and sufficiently intelligent and willing to adhere strictly to a prolonged medical regimen, such treatment should certainly be employed, unless and until complications or surgical indications supervene. For those, however, who are economically unable or not sufficiently intelligent or willing to cooperate, the prescribing of medical treatment is too frequently a waste of time and delays eventual rehabilitation. Such circumstances well might be given consideration among the generally accepted surgical indications—hemorrhage, obstruction and perforation.

An ulceration in the stomach might better be considered an indication for surgical treatment until proved otherwise. In young persons with small uncomplicated gastric ulcerations and roentgenologic evidence of response to medical treatment within two or three weeks, surgical intervention would seldom be warranted. As the age of the patient increases, however, the danger of even small gastric ulcerations being malignant increases, and greater caution should be exercised. In the

middle-aged or older patient, even the small gastric ulceration, unless it shows roentgenologically prompt diminution in size under treatment, and assuredly the larger ulceration are potentially malignant and should be excised.

SUMMARY

A brief review of some of the more recent statistical studies of persons medically and surgically treated for peptic ulcer was made for purposes of comparison with a similar study of patients with peptic ulcer at the University of Virginia Hospital. At that institution, from 1918 to 1928, 286 persons were treated, 66 for gastric and 220 for duodenal ulcerations. Most of the patients were from rural districts and the smaller towns and cities and presented peculiar problems because of their economic status, mode of living and dietary habits and limitations.

The general statistics were similar to those generally given, except that there was twice as high an incidence of peptic ulceration in the white as in the Negro race, and that the ratio of duodenal to gastric ulceration was only about three and one-half to one rather than a higher ratio, as much as ten to one, given by some writers.

The late results (after from two to twelve years) of medical and surgical treatment in 164 patients were ascertained by follow-up. They were classified under excellent, good, fair and poor general results after the symptomatic and economic results were estimated and the dietary limitation and the use of alkali necessitated were recorded.

Of 33 patients with gastric ulcer successfully followed, 25 had been treated medically and 8 surgically. Of the 25 treated medically, 3 had subsequently died of carcinoma of the stomach and 3 of unspecified causes. Of the 19 survivors, slightly more than one half reported satisfactory results. Of the 8 treated surgically one had subsequently died of some gastric disorder, but all of the 7 survivors reported satisfactory results.

Of 131 patients with duodenal ulcer successfully followed, 85 had been treated medically and 46 surgically. Of the 85 treated medically, 2 had subsequently died from the ulcer, 2 from other causes and 2 from unspecified causes. Of the 79 survivors a few less than one half reported satisfactory results, and 6 had subsequently resorted to surgical treatment because of the persistence of symptoms. Of the 46 treated surgically, 2 had died subsequently of unspecified causes and 2 of causes other than ulcer. Of the 42 survivors more than three fourths reported satisfactory results. In 3 patients gastrojejunal ulceration apparently developed.

In the type of patient studied the results of the medical management of peptic ulcer were appreciably less satisfactory than the results of the surgical treatment. To obtain satisfactory results, those treated medically had had to adhere much more strictly to dietary regulation and the use of alkalis than those treated surgically. Some criteria for the choice of treatment have been briefly alluded to.

EFFECT OF STIMULATION OF VISCERAL NERVES ON CORONARY FLOW IN DOGS

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In this paper, the results of a study of the effect of stimulation of the visceral nerves and distention of the stomach, the lower part of the esophagus and the gallbladder will be reported. The results of such a study are obviously not only of academic interest but also of clinical interest, because of the relative frequency of attacks of coronary thrombosis and angina pectoris after the ingestion of food and accompanying gaseous distention.

The study of the effect of visceral excitation on coronary flow appears at first sight to be simple and clearcut. However, because a number of other factors are concerned in regulating the coronary circulation, the problem is somewhat involved. The chief factor regulating coronary flow, which has been recognized as such by all investigators of coronary circulation, is blood pressure.[1] The rise and fall of blood pressure and the rise and fall of coronary flow are directly parallel. The heart rate appears to have no effect on coronary flow. Some observers have noted a decreased flow with an increased heart rate produced by means of an increase in temperature. But since it is known that temperature has a direct effect on the coronary vessels and since other methods of changing the heart rate, that is, by induction shocks and by heating and cooling the sino-auricular node, are without effect, it seems that there is no pure frequency change which directly influences coronary flow. Whatever the effect of heart rate on coronary flow may be, it seems to be determined by changes in the duration and the strength of ventricular contraction. Increased "tone" of the heart is thought not to increase the flow. But "dilatation" of the heart does increase it. Lack of oxygen and an increase in carbon dioxide augment the flow. Metabolites appear to have no effect in the heart-lung preparation. Whether or not they do in the whole animal has, as yet, not been determined. Another point that must be taken into consideration is that a progressive increase in coronary flow frequently occurs during

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1. Anrep, G. V.: Physiol. Rev. **6**:596, 1926.

the course of an experiment. We have observed this as have others. It has been ascribed to a loss of "tone" or "dilatation" of the heart which favors an increased coronary flow.[1]

The coronary arteries have a rich innervation. The denervation experiments of Woolard [2] show that the coronary arteries up to their finer ramifications receive a double innervation. The larger arterial branches are innervated by the vagus and sympathetic fibers to about an equal extent, while the innervation of the smallest branches is predominantly vagal in origin.

The aforementioned points were kept in mind as factors to be taken into consideration in a study of the effect of excitation of visceral nerves and organs on coronary flow.

The method of Morowitz and Zahn [3] was used on dogs. The blood drainage of the heart flowing into the coronary sinus (60 per cent of the entire amount) was collected by means of a Morowitz cannula, as modified by Gilbert and Fenn,[4] which was placed in the sinus. The cannula was connected through rubber tubing to an inlet at the bottom of a large test tube, the tube being provided with a similar outlet and with a float. The inflow causes the float to rise, making a tracing on the smoked drum at the same time as blood pressure and time records are made. The tube was emptied when full, and the blood returned to the animal through the femoral vein after passage through loops of glass coils immersed in water at a temperature slightly higher than that of the body so as to keep the temperature of the blood as nearly normal as possible. The rate of return of the blood was regulated so that the inflow would be about as rapid as the outflow. Heparin (12 mg. per pound of body weight) was used to prevent coagulation. Pentobarbital sodium anesthesia was used. The heart was kept from drying by closing the chest except when the nerves in the chest were stimulated, and then physiologic solution of sodium chloride at 34 C. (93.5 F.) was applied to the heart.

EXPERIMENTAL RESULTS

Stimulation of Intact Vagus Nerve Below Heart on Esophagus Above Diaphragm and on Stomach in Region of Cardia.—The intact nerve at the level of the esophagus and of the stomach was stimulated with an induced current. This was done primarily to obtain at the same time peripheral effects, contraction of the stomach and central reflex effects. In order to stimulate the intact nerve it was simply dissected free for about 1 inch (2.5 cm.) and the electrodes applied. (For all electrical stimulation experiments a Harvard inductorium with two dry cells and the secondary coil at 4 cm. was used.)

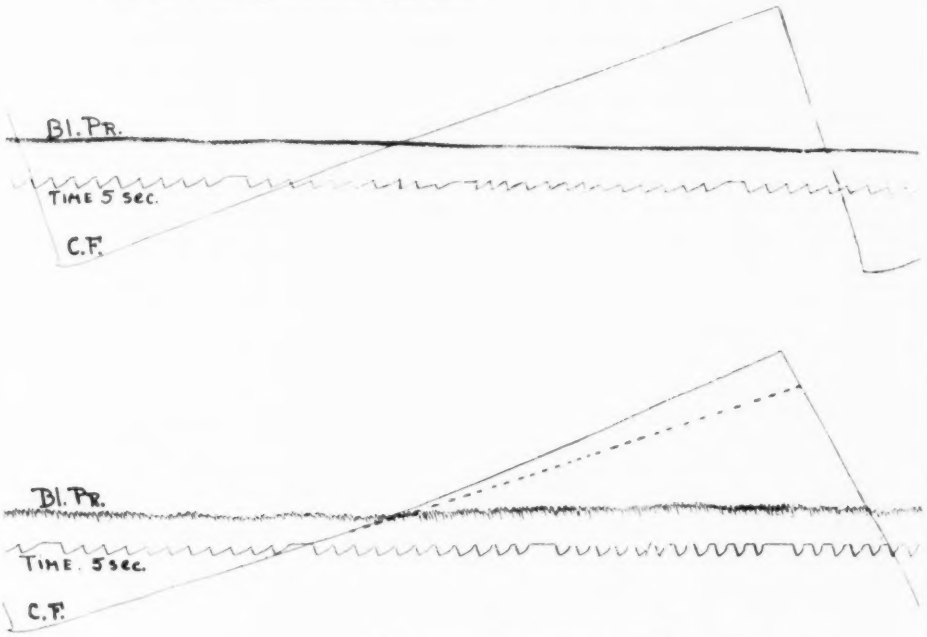
Twenty-six experiments were performed. There was no detectable difference in the results when the intact nerve was stimulated on the

2. Woolard: J. Anat. **60**:345, 1926.

3. Morowitz and Zahn: Deutsches Arch. f. klin. Med. **116**:364, 1914.

4. Gilbert, N. C., and Fenn, G. K.: Effect of the Purine Base Diuretics on the Coronary Flow, Arch. Int. Med. **44**:118 (July) 1929.

esophagus or on the stomach. In six experiments the blood pressure was elevated and the coronary flow, of course, increased. In two of ten experiments an increase (25 and 68 per cent) in coronary flow was associated with a fall in blood pressure. In four of five experiments the coronary flow was increased without a change in blood pressure, the range of increase being from 10 to 45 per cent. In one of five experiments the coronary flow was decreased (24 per cent) without a change in blood pressure.



STIM. CENT. END GASTRIC VAGUS

This figure shows that stimulation of the central end of the gastric vagus may lead to an increase in coronary flow. The upper tracing is the control flow. The ascending line labeled "*C.F.*" is made by the float which rises as the blood from the coronary sinus fills the tube in which the float rides. In the upper tracing it is to be noted that the float rises uniformly. In the lower tracing just after the stimulation of the vagus it is to be noted that the float rises more rapidly, denoting an increase in coronary flow.

It is evident from these results that stimulation of the intact vagus below the heart may cause an increase in coronary flow, since a decrease occurred in only one of the twenty-six experiments, and since an increase in flow was observed. Not only did no change in blood pressure occur, but in two of ten instances an increased flow resulted during a fall in blood pressure.

Stimulation of Central End of Sectioned Vagus Nerve Below Heart.—Twenty experiments were performed as in the preceding group, except that the vagus was sectioned and the central end stimulated.

In four experiments an increase in coronary flow was associated with a rise in blood pressure. In two of four experiments an increase (5 and 10 per cent) in coronary flow occurred, with a decrease in blood pressure. In one of four experiments a decrease in flow resulted with a decrease in blood pressure, and in one of four experiments a decrease in blood pressure was not associated with a decrease in flow. In three of four experiments the flow increased without a change in blood pressure, the increase ranging from 14 to 53 per cent.

These results are essentially the same as those obtained in the preceding group, and show that excitation of the gastric and esophageal vagi induces an increase in coronary flow.

Stimulation of Right Splanchnic Nerve Below Diaphragm.—An attempt was made to stimulate the right splanchnic nerve centrally with a weak current without obtaining a rise in blood pressure, but at the same time obtaining a change in coronary flow. This could not be accomplished in all dogs. Thirteen experiments were done. In three experiments the blood pressure rose with the usual increase in coronary flow. In two of four experiments a fall in blood pressure was associated with an increase (12 and 16 per cent) in coronary flow. In two experiments an increase (20 and 52 per cent) in coronary flow was not associated with a change in blood pressure. A decrease in coronary flow was associated with a decrease in blood pressure in two experiments.

In addition to these experiments, the nerves along the cystic and common bile ducts and splenic vessels and the celiac plexus were stimulated. Invariably no change in coronary flow resulted that could not be accounted for as being due solely to a rise or fall in blood pressure.

From the results in this group of experiments it is evident that if any change in coronary flow results from stimulation of the visceral nerves which cannot be accounted for by fluctuations in blood pressure, it is always in the direction of an increase in coronary flow.

Distention of Esophagus, Stomach and Gallbladder.—The lower end of the esophagus, the stomach and gallbladder were markedly distended by fixing a balloon in place within the lumen. Thirteen experiments were performed. Since the results were essentially the same, regardless of the viscus distended, they may be grouped. In five experiments, increase in coronary flow was associated with a rise in blood pressure. In one of four experiments, the coronary flow increased (32 per cent) in the presence of a slight fall in blood pressure. An increase (27 per cent) in coronary flow occurred in one of two experi-

ments in which there was no change in blood pressure. Decreased coronary flow occurred in one of two experiments in which the blood pressure did not change. The decrease was definite (8 per cent) and occurred when the gallbladder was distended.

Stimulation of Peripheral Vagus in Neck After Atropine.—Although we were not directly interested in the question of the vagal control of the coronary circulation, five experiments were performed in which after the administration of atropine the peripheral left vagus was stimulated about 1 inch below the thyroid cartilage. In four of the five experiments, increased coronary flow resulted either in no change (two experiments) or in only a slight decrease in blood pressure (two experiments). In one a decrease (13 per cent) in coronary flow occurred in the presence of a slight rise in blood pressure. These results show only that a variation in the coronary response to stimulation of the vagus nerve in the dog occurred in our experiments.

COMMENT

We agree with Greene,[5] who used the same method we have employed, that it is difficult to demonstrate a decided decrease in coronary flow in the dog on stimulation of the vagus. These observations are not necessarily to be taken as contradictory to the results of Anrep and Segall [6] and of Wiggers,[7] who employed different methods for studying coronary flow. The variation in results may be due to the presence of different types of fibers in the vagus which may vary from one dog to another in regard to the number of each type in each vagus nerve trunk and the relative numbers of these fiber groups found at different levels in the vagus trunk after it leaves the ganglion nodosum. In this respect, the recent work of Morgan and Goland [8] is pertinent. No one has stimulated the vagus in the region of the ganglion nodosum to ascertain whether the vasoconstrictor nerves are in the vagus trunk before sympathetic fibers join it, and the fact that Wiggers after the use of atropine in the dog obtained a decrease of coronary flow on stimulating the vagosympathetic pharmacologically indicates that the vasoconstrictors may be sympathetic rather than parasympathetic.

Although we had expected to observe coronary constriction quite regularly on excitation of the abdominal viscera or nerves leading from them, we failed to do so. In only two of forty-nine experiments did we observe a decreased coronary flow on distending the viscera or on stimulating the central end of the vagi or splanchnic nerves which

5. Greene. J. Missouri M. A. **28**:466, 1931.
6. Anrep and Segall: J. Physiol. **61**:215, 1926.
7. Wiggers: Am. J. Physiol. **24**:391, 1909.
8. Morgan and Goland: Am. J. Physiol. **101**:274, 1932.

could not be accounted for by a change in blood pressure. In these two experiments the constriction was slight, being 8 and 24 per cent, when compared to the dilatation which sometimes amounted to 68 per cent. This is essentially in agreement with the findings of Greene, the only difference being that he found that if the stimulation of the sensory nerves from the abdominal viscera was intense, a diphasic reaction resulted which was characterized by coronary dilatation followed by constriction. This we failed to observe.

When we seek to interpret these results on the dog in regard to the relation of visceral distention and excitation to angina pectoris in man, we can only arrive at the same opinion expressed by Sutton and Lueth [9] and Greene, namely that the failure of reflex coronary dilatation under conditions which augment cardiac activity accounts for the association of angina with visceral excitation. Visceral distention and irritation increase the rate and work of the heart, and normally a reflex dilatation of the coronary vessels should occur. If dilatation does not occur, angina is likely to occur because of partial asphyxia or an inadequate supply of oxygen to the cardiac muscle. It is analogous to the concept of "effort angina," a "visceral effort angina" analogous to the so-called somatic "effort angina." We accept the theory that reflex coronary constriction may be a factor, but maintain on the basis of our results on the dog that the failure of the reflex dilator mechanism plays a more important rôle than the constrictor mechanism. In regard to the association between the ingestion of a meal and the occurrence of coronary thrombosis, it is just as likely that a portion of an atheromatous plaque might be dislodged as a result of the increased cardiac activity incident to digestion and of an attempt on the part of the coronaries to dilate as to constrict.

CONCLUSIONS

1. The usual result of stimulating the central end of sensory nerves innervating the upper abdominal viscera or of distending the viscera on coronary flow is an increase in flow. An unquestionable decrease in flow occurred in only two of forty-nine tests, whereas an unquestionable increase in flow occurred in nineteen of thirty-nine tests.

2. In the dog reflex coronary dilatation is more readily demonstrated than reflex constriction.

3. We are inclined to accept the view of Greene, who has performed similar experiments on the dog, namely, that the failure of the reflex coronary dilator mechanism most likely accounts for the association of angina pectoris with visceral distention or excitation.

9. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

AURICULAR FLUTTER WITH COMPLETE AURICULO-VENTRICULAR BLOCK IN A PATIENT WITH CORONARY DISEASE

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Of singular interest is the striking abnormality of rhythm exhibited in electrocardiographic tracings in the group of cases known as auricular flutter. This peculiar rhythm is a finding strictly within the domain of electrocardiography, since the clinical signs exhibited by patients with such a condition are very difficult if not impossible of detection through any other means. The reason for diagnostic failure clinically in the majority of instances of auricular flutter are obvious to those who are at all familiar with the nature of this disturbance of rhythm. Both the ear and the palpating finger at the wrist are greeted by a perfectly regular sequence of contractions, except where there exists an inconstant degree of auriculoventricular block; in most of these the ventricular rate is only moderately accelerated. It is true that the tonal quality of the heart sounds is rather altered, but such finesse in clinical differentiation belongs to diagnostic skill and acumen of the highest order only. For all practical purposes, therefore, the recognition of auricular flutter at present rests strictly with the electrocardiogram.

It is not our purpose here to delve into the intricacies of auricular flutter as a clinical or electrocardiographic entity. We merely wish to add to the literature a very interesting and uncommon case of auricular flutter with coexisting complete auriculoventricular block in a patient with coronary disease.

REPORT OF A CASE

History.—H. C., a man, aged 60, a native of Germany, a shoe clerk, presented an unimportant family history, both parents having died at an advanced age. His seven brothers and sisters were all living and well. There was no history of heart disease, nephritis, cancer, tuberculosis, diabetes, insanity or chronic alcoholism. The outstanding complaints were extreme fatigue, marked shortness of breath and a peculiar sensation in the chest, which the patient described singularly well as that of a "bird flapping its wings" within it.

From Medical Service A., of Dr. Aaron E. Parsonnet, Newark Beth Israel Hospital.

His previous medical history was uneventful, except for the usual diseases of childhood. The surgical history consisted of the removal of a "growth" from his colon six or seven years before the present examination, the nature of which could not be ascertained. He was told some years ago that he had a "slow pulse." He had occasional eructations after meals. About two years ago he had one attack of diarrhea with vomiting, and was confined to bed for ten days. For the past five years he had a marked nocturia, being compelled to get up four or five times during each night. He lost about 40 pounds (18.1 Kg.) in weight in the past six months, during which time fatigue became one of the most prominent symptoms.

He had been married fourteen years, but had no children; his wife always enjoyed perfect health and gave no history of any miscarriages.

He never exercises, drinks tea and coffee sparingly, is a teetotaler, and has smoked three cigars daily for the past thirty years. He has always been a poor sleeper, averaging from four to five hours of interrupted sleep a night for the past twenty years.

The illness began about six months ago when the patient was seized during the night with a severe, lancinating pain in the right side of the chest, extending roughly from the second to the seventh ribs and radiating to the back into the subscapular and right lumbar regions. Sleep was almost impossible because of the practically nightly occurrences of these seizures, which were further aggravated by paroxysms of severe and prolonged coughing. The expectoration—ordinarily greenish, viscid and copious—became streaked with blood during the last two months. He had noted a marked shortness of breath, tenderness in the epigastrium and right upper quadrant, with a sensation of weight in the abdomen. The lower extremities, from the knees down, became markedly swollen during the past three weeks, so much so that the patient was frequently forced to go to work with his shoes unlaced.

Although the nocturia had increased to such a degree that sleep was out of the question, even when free from pain, micturition became exceedingly difficult; at no time in the last three weeks did he feel that his bladder was completely emptied. Anorexia became marked, and the patient was rather apprehensive of taking food because of the distress which followed meals with almost clocklike punctuality. Constipation at this time became obstinate. About one week before the patient presented himself for examination, fatigue had become so pronounced that he was obliged to go to bed for a few days. His peace of mind was considerably disturbed by the fact that fellow employees told him that he looked thin, pale and drawn.

Physical Examination.—The patient was 5 feet, 7 inches (170.2 cm.) tall, and weighed 138 pounds (62.6 Kg.). He was chronically ill and cachectic in appearance, with marked cyanosis of the lips and mucous membranes. The skin was free from eruption, and was cold and clammy to the touch. The flabby state of his musculature indicated a recent loss of weight. Oral examination revealed marked dental sepsis. The nasopharynx was normal. The tongue was geographic and thickly coated; it protruded in the midline, and no fissures, atrophy or tremors were noted. The larynx was freely movable; the thyroid gland was not enlarged and was normal in consistency. There was clear transillumination of all sinuses. The eyes reacted to light and in accommodation; the pupils were regular, and both palpebral fissures were equal. There was no exophthalmos, nystagmus or strabismus; the conjunctivae were moderately injected. The fundi disclosed moderately increased tortuosity of the arteries. All superficial glands were negative. The reflexes were negative except for moderately increased knee jerks. The blood pressure taken repeatedly averaged 150 systolic over 60 diastolic.

The heart was markedly enlarged to percussion in all its diameters, but especially in the region of the great vessels. All heart sounds were muffled and distant. The second sounds at the aortic and pulmonic areas, although markedly subdued, were equal in intensity. There were no murmurs, shocks or thrills. The rhythm was perfectly regular with a ventricular rate of 38 beats per minute; there was no apparent pulse deficit. The rate was uninfluenced by a very moderate exercise test (spirometer), although the patient showed a marked dyspneic reaction following it, pointing to a serious loss of myocardial reserve.

The chest was of the emphysematous type; there were no abnormal pulsations visible or palpable. Many moist râles were heard at the bases of both lungs posteriorly.

Of interest is the examination of the abdomen. It was distended, tympanitic and decidedly tender to pressure. A hard unyielding mass was felt in the epigastrium; this seemed to be confluent with the liver and spleen, the lower border of which could be palpated with ease on deep inspiration. (In view of the past surgical history, we felt that this mass was metastatic in character.) The liver itself was very large and exhibited weak systolic pulsations; its increase in size, however, was due mostly to cardiovascular stasis.

The genito-urinary tract disclosed no abnormalities except an exceedingly large and boggy prostate. Large protruding and engorged hemorrhoids were present.

The lower extren. ties were swollen and pitted on pressure.

Fluoroscopic examination fully corroborated the findings in the chest. The transverse diameter of the chest measured 30 cm., with a maximum transverse cardiac diameter of 19.5 cm. The pulmonary fields were essentially clear. Diaphragmatic excursions were weak, small and halting; no adhesions were noted. The aortic shadow was markedly widened.

Laboratory Data.—The Wassermann and Kahn tests were negative. The urine showed 2 plus albumin with occasional granular casts and frequent pus cells. Many calcium oxalate crystals were noted. The blood count showed a hemoglobin of 56 per cent, with 3,200,000 red blood cells; there were 6,800 white blood cells and the differential count showed 62 polymorphonuclears, 26 lymphocytes, 11 mononuclears and 1 eosinophil. All cells showed marked poikilocytosis.

Chemical analysis of the blood showed a slightly increased urea nitrogen of 22.5, creatinine, 1.6 and sugar, 91 mg., per hundred cubic centimeters.

Any interesting points which may have been brought out in the personal or physical history of this patient are far overshadowed by the electrocardiographic findings. The series of tracings presented cover a period extending from July 11, to July 18, 1932. Further studies were abruptly terminated by the patient's sudden death several hours after the last tracings had been recorded.

Figure 1 shows an auricular flutter with a ventricular rate of 40 and a constantly maintained auricular rate of 230 beats per minute, approximating roughly a 6:1 rhythm. There is a distinct shift of the axis to the left, with leads II and III exhibiting a downward direction of the Q R S complexes. The Q R S complexes are also slurred and splintered in the second and third leads.

In figure 2, taken two hours later, similar changes occur, except for an acceleration of the auricular rate to 430 beats per minute, the ventricular rate remaining the same as in figure 1. This was followed by another tracing three hours later, but it showed no appreciable changes.

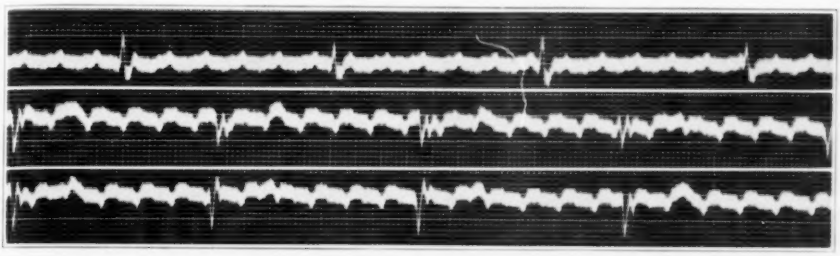

Fig. 1.—Auricular flutter with an approximate 6 : 1 rhythm.

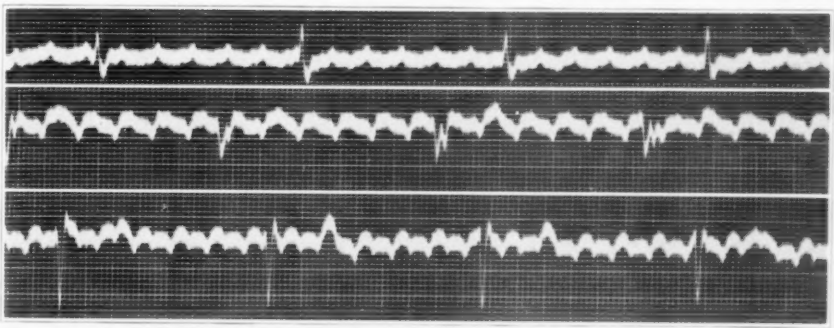

Fig. 2.—Same as figure 1, with an auricular rate of 430 beats per minute. Note the slow ventricular rate of 40.

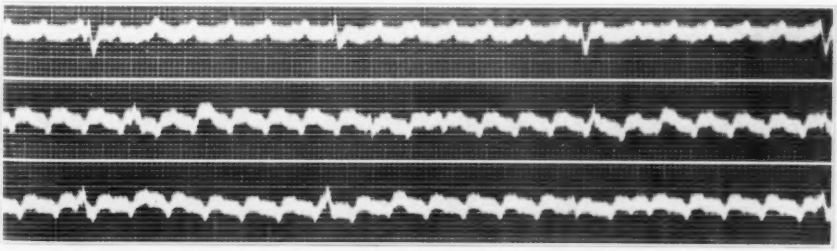

Fig. 3.—Shift of directional axis to the right.

Figure 3, taken on the following day, exhibits a striking change in the directional axis, assuming now a definite right axial rotation. The auricular rate is again reduced to 230 beats per minute, while the ventricular rate remains unaltered.

Figure 4, taken two hours later, shows a change in contour of the various Q R S complexes in lead 1; some are directed upward, while others point definitely downward. The auricular rate in lead III is once more accelerated to 430 beats per minute.

To obtain a clearer conception in detail of the electrocardiographic findings, a double speed camera tracing was taken (fig. 5). Here again we observe an unorthodox departure from the usual; the Q R S complexes are directed upward in leads I and III, and downward in lead II. The uncommon auricular rate of 440 beats per minute is more clearly exhibited in lead III of this graph. There is no longer any doubt as to the rate of the auricular waves in this tracing; these are now clear and definite.

Between July 12 and July 18, the patient was much too ill for further electrocardiographic studies. Figure 6 was obtained on July 18 and shows a downward deflection of the Q R S complexes in leads I and III, with an occasional Q R S complex in lead III assuming an upward direction. Otherwise there are no spectacular changes.

Between this and the last tracing, the clinical picture of the patient became strikingly aggravated. The blood pressure no longer registered instrumentally, and complete cardiac collapse ensued. The patient suffered from extreme stenocardia with the pain radiating down both arms; he felt cold and clammy, perspired profusely and became much agitated and dyspneic. Figure 7, taken only a few hours before death, showed a right deviation of the electrical axis, the same rapid auricular rate in lead III previously noted, but in addition exhibited bizarre complexes following the Q R S in leads II and III. These resemble in many respects the typical T wave alterations which have been described as occurring in coronary occlusion with infarction.

To facilitate the analysis of the seven electrocardiograms presented, we have graphically shown the various outstanding features of the tracings relating to the auricular and ventricular rates, the changes in axis deviation and the various alterations in the Q R S complexes in the table.

The first description of auricular flutter we owe to MacWilliam,[1] who as early as in 1887 described such a rhythm after faradizing the auricles of dogs. This he appropriately designated as "auricular flutter." However, Ritchie,[2] in 1905, before the use of the electrocardiograph

1. MacWilliam, J. A.: J. Physiol. **8**:296, 1887.

2. Ritchie, W. T.: Auricular Flutter with Complete Heart Block, Proc. Roy. Soc. Edinburgh **25**:1085, 1905.

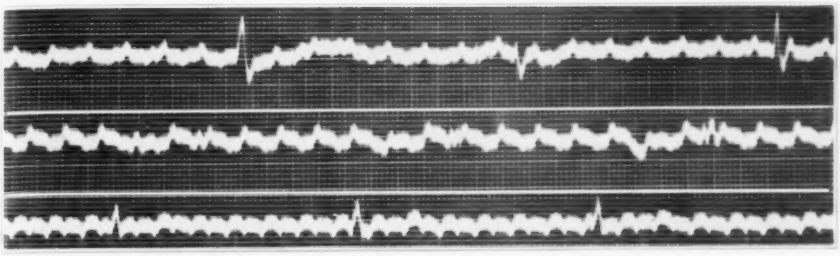

Fig. 4.—Note the directional changes of Q R S complexes in lead I.

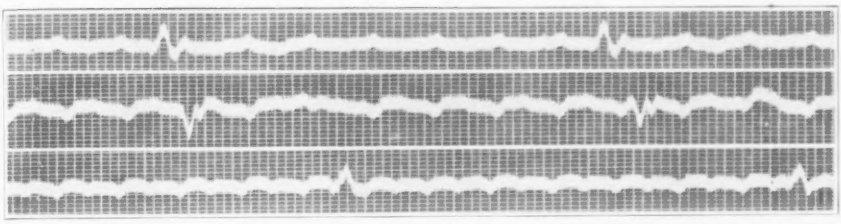

Fig. 5.—Tracing taken at double speed; rapid auricular rate clearly exhibited in lead III.

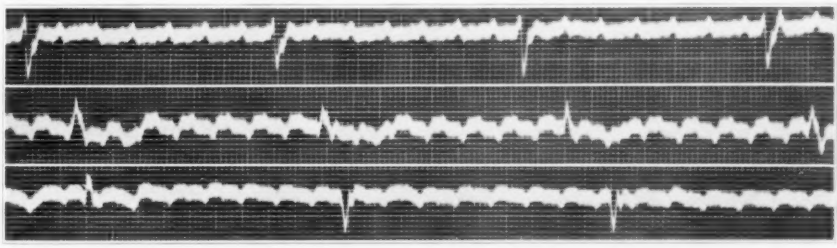

Fig. 6.—Undetermined axis deviation.

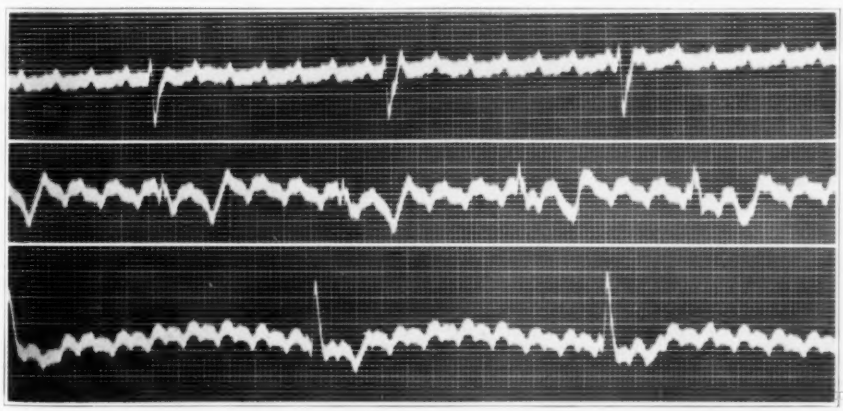

Fig. 7.—Leads II and III showing T wave changes usually associated with coronary occlusion with infraction.

became general, was enabled to demonstrate polygraphically the presence of this abnormal rhythm because of the extreme slowness of the ventricular rate, which was unquestionably due to complete heart block. Four years later, the same author, in collaboration with Jolly,[3] again recorded the occurrence of auricular flutter with auriculoventricular dissociation electrocardiographically. Since that time only a few articles have appeared in the medical literature dealing with this rare combination of abnormal rhythms; these were by Hart,[4] De Boer,[5] Strauss,[6] Henderson and Rennie,[7] Roth,[8] Willius,[9] and Lian and Viau.[10] Roth,[8] in his book on "Cardiac Arrhythmias," dismisses this subject with a single tracing but no discussion. Willius,[9b] in 1929, reported only a single instance of auricular flutter with established complete heart block occurring in 168 cases of auricular flutter, observed on taking 40,000

Analysis of Electrocardiograms Discussed

Number of Tracing	Auricular Rate per Min.	Ventricular Rate per Min.	Axis Deviation	Q R S Interval, Sec.	Additional Data*
1	230	40	Left	0.08	
2	230 to 420	40	Left	0.08	
3	230	40	Right	0.06-0.08	One Q R S complex in lead I directed upward
4	220 to 430	40	Undetermined	0.06-0.10	One Q R S directed downward and two Q R S's upward in lead I
5	220 to 440	40	None	0.08	
6	220	40	?	0.06-0.10	Q R S directed downward in leads I and III with one Q R S complex upward in lead III
7	220 to 440	40	Right	0.06-0.10	T waves characteristic of those found in coronary occlusion

* Splintering of Q R S complexes occurs in all tracings.

3. Jolly, W. A., and Ritchie, W. T.: Auricular Flutter and Fibrillation, Heart **2**:177, 1909.

4. Hart, T. S.: Abnormal Myocardial Function, New York, The Rebman Company, 1917, p. 122, fig. 89; p. 125.

5. De Boer, S.: Auricular Flutter and Auricular Fibrillation in Total Heart Block, Nederl. tijdschr. v. geneesk. **1**:550, 1924.

6. Strauss, A. E.: Heart Block, Auricular Flutter and Adenoma of the Thyroid, M. Clin. North America **11**:487, 1927.

7. Henderson, J., and Rennie, J. K.: Auricular Flutter: A Case with Complete Heart Block, Glasgow M. J. **108**:355, 1927.

8. Roth, I.: Cardiac Arrhythmias, New York, Paul D. Hoeber, Inc., 1928, p. 201, fig. 71.

9. Willius, F. A.: (*a*) Auricular Flutter with Established Complete Heart Block, Am. Heart J. **2**:449, 1927; (*b*) Clinical Electrocardiograms, Philadelphia, W. B. Saunders Company, 1929, p. 62.

10. Lian, C., and Viau, O.: Electrocardiography of Auricular Flutter and Bradycardia Through Complete A-V Dissociation, Arch. d. mal. de cœur **23**:514, 1930.

routine electrocardiograms. It is interesting to note in this connection that even in the most recent exhaustive treatise on heart disease by White,[11] only passing mention is made of this combination, further emphasizing its rarity.

It would not be amiss to point out that the controversy concerning the causative factors and mechanism instrumental in the production of auricular flutter has not been completely settled.[12] Although there are still some adherents to the theory that this rhythm is brought about by showers of auricular extrasystoles which are being initiated at such a rapid rate that the ventricles can no longer keep up with the accelerated rate from above, the majority of cardiologists today are in thorough accord with the circus movement theory of Lewis,[13] to which the authors unequivocally agree. From all standpoints, the latter seems to be by far the most plausible.

Of greater interest here is the unusual rapidity of the auricular rate which so closely approaches that seen in auricular fibrillation and yet maintains the perfect regularity and rhythmicity of flutter. If we are to allow that auricular fibrillation and flutter are both governed by the mechanism of circus movement, the ring of heart muscle about which the impulse circles in this particular case must of necessity be of a much smaller diameter than that existing in the usual types of flutter, yet large enough so that when the initial impulse reaches its starting point it finds the heart muscle just recovered from its refractory period. Thus, the circus remains unbroken and is enabled to continue.

Of interest also, as pointed out previously, is the rare combination of auricular flutter with complete heart block. The history of our patient makes us rather certain that complete auriculoventricular block preceded the development of auricular flutter by many years. The patient had mentioned the fact that as long as ten years ago he was refused life insurance because of a "slow pulse." Unfortunately, he was not specific enough as to the exact rate; his wife, however, volunteered the additional information that two years ago he had several spells of unconsciousness; this in the light of present knowledge may be suspected of fitting into the Stokes-Adams syndrome. Their occurrence antedated the complaint of fluttering sensations in the chest described in our patient's personal history. At best, it must be remembered that heart block is a much more common phenomenon than auricular flutter,

11. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

12. Parsonnet, A. E., and Hyman, A. S.: Applied Electrocardiography, New York, The Macmillan Company, 1929, p. 102. Hyman, A. S., and Parsonnet, A. E.: The Failing Heart of Middle Life, Philadelphia, F. A. Davis Company, 1932, p. 312.

13. Lewis, T.: Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1925.

and also that auricular flutter seldom, if ever, is engrafted on a previously intact heart musculature. Hart,[4] in a discussion of the pathologic picture of auricular flutter, reports autopsy observations on three men of 51, 54 and 55 years of age, respectively, in each of whom little normal heart muscle could be found. They showed sclerosis of the coronary arteries with old infarcts invading the left ventricular walls. Another point that practically proves a preexisting damage to the heart muscle is the clearcut clinical picture of coronary occlusion with infarction which caused our patient's sudden death.

In a careful review of the literature we have been able to find but a single case with an auricular rate approaching in rapidity that exhibited in this report. It is the one reported by Hart,[4] as a 4:1 flutter with an auricular rate of 492 and a ventricular rate of 123; however, this was not a case of complete heart block. We have also failed to note even a single instance of auricular flutter with coexisting complete auriculoventricular block occurring in a patient with an undoubted coronary occlusion with infarction, graphic evidence of which is seen in figure 7.

SUMMARY

A case of auricular flutter with an unusually high auricular rate is reported. This condition was superimposed over a complete dissociation of the auricles and ventricles in a patient who subsequently died with all the classic manifestations of coronary occlusion and infarction. Of singular interest is the rarity of such a combination of abnormal rhythms, the extremely high auricular rate, the rapid changes of axis in the various leads, the clear demonstration of flutter configuration in lead I and finally, the typical T waves as seen in coronary disturbances. The fact that few such cases have been reported in the literature has prompted us to publish this one.

STANDARDIZATION OF CHEST LEADS AND THEIR VALUE IN CORONARY THROMBOSIS AND MYOCARDIAL DAMAGE

ARTHUR M. HOFFMAN, M.D.
AND
EVERETT DELONG, M.D.
LOS ANGELES

Interest in the use of chest leads in the diagnosis of coronary thrombosis was stimulated by Wolferth and Wood.[1] In a patient with normal standard leads with a clinical picture of coronary thrombosis, they found a striking abnormal deviation of the S-T interval from the isoelectric line in tracings taken with electrodes over the anterior and posterior surfaces of the chest. A second patient showed only a minor deviation from the normal in lead I and a more pronounced deviation in the chest lead, or lead IV. These changes they also found in experimentally produced occlusion of the coronary arteries.[2]

They state that "if conclusions are to be drawn from minor variations in the contour of the tracings in lead IV, the relation of electrodes to the heart should be kept constant. We paid no attention to minor variations in the position of the electrodes and have not drawn conclusions on these grounds." In our first attempts to take chest leads, we encountered marked rather than minor variations of the P, Q-R-S and T complexes in lead IV.

A few other observers personally stated that they had encountered the same difficulty. They, therefore, attempted to disparage the value of the chest lead.

We, accordingly, have attempted to standardize the curves obtained in chest leads by standardizing the position on the wall of the chest. We believe we have demonstrated the feasibility of obtaining uniform tracings by a standard technic. We present this technic in a series of one hundred and twenty-five normal control cases as well as in a series of clinical cases of coronary thrombosis and other forms of myocardial damage.

From the Santa Fe Coast Lines Hospital, Los Angeles.

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30 (Jan.) 1932.

2. Wood, F. C., and Wolferth, C. C.: An Electrocardiographic Study of Experimental Coronary Occlusion: The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Current, J. Clin. Investigation **9**:815 (July) 1932.

NORMAL CONTROLS AND POSITIONS

As it has been demonstrated by Lewis and Wilson that changes in the position of the electrodes on the wall of the chest produce changes in the auricular-ventricular deflections of the electrocardiographic tracings, we have selected five positions for placing the electrodes. We feel that these five positions cover the anterior surface of the heart quite thoroughly, and are as follows:

Position A.	Anterior:	In the center of the chest at the level of the fifth to the sixth interspace.
	Posterior:	In the center of the back on the level with the anterior electrode.
Position B.	Anterior:	Over the position of the maximum impulse of the heart.
	Posterior:	On the left side of the spine between it and the scapula at the level of the spine of the scapula.
Position C.	Anterior:	On the left side of the chest over the second interspace about 2 to 3 inches from the midsternal line.
	Posterior:	Same as Position B.
Position D.	Anterior:	Over the position of the maximum impulse.
	Posterior:	On the left side of the back below the angle of the scapula on the level with the anterior electrode.
Position E.	Anterior:	In the center over the precordia.
	Posterior:	On the left side of the back on the level with the anterior electrode.

Our first attempts to attain chest leads were by using the usual 4 by 6 inch arm electrodes placed over the precordia anteriorly and over the back posteriorly. The right arm wire goes to the anterior electrode and the left arm wire to the posterior electrode. We found considerable variation in the size and shape of the P, Q-R-S and T complexes. We then used a smaller, hollow, round copper cup, 2 inches in diameter, as suggested by the Sanborn Company. This was filled with a copper sponge "choreboy." These electrodes gave strikingly ununiform tracings when placed in various positions on the chest. The influence on the tracings of imperfect contact and lack of proper insulation was great. They gave results unreliable for clinical use.

Because of the consistently poor results with the foregoing electrodes, we have devised a new type. These we will describe briefly.

They consist of slightly concave circular copper plates, 2 and 4 inches in diameter. On the convex side is the terminal, situated in the center, welded to the plate at a right angle. Over the plate fits a flannel cloth which is held secure by a draw string. When one is ready to use it, the electrode is soaked in hot salt solution in the usual manner or contact made without the flannel cloths but with a special conducting paste.

It is important that the electrode be exceptionally well insulated, as this can be a great source of error and disturbance. Hard rubber is satisfactory. However, we would recommend that the steel spring clamp that holds the electrodes on to the chest have a bakelite mold on each end about 5 or 6 inches long. These will entirely insulate the electrodes from each other, as well as insulate the clamp from the body in case of accidental contact (fig. 1).

We found that the 2 or 4 inch electrodes worked equally well with resistances under 1,000 ohms and gave curves which are practically identical. We believe that

the uniform results produced by this style of electrode are due to good insulation and good contact with the patient. They also are easy to make, inexpensive, and no troube to use. They fit the chest snugly, owing to the slightly raised center, and are relatively trouble-free. Figure 2 illustrates the curves obtained in positions A, B, C, D and E by these electrodes on two normal subjects. It will be observed that the T wave is normally inverted. This is only an arbitrary matter and can be changed by reversing the lead wires to the machine. The interpretation of the tracings so far as the T wave is concerned is the reverse of that of the routine leads. Thus a normal chest lead has an inverted T, while the normal routine lead has an upright T. We have also confirmed the statement of Wilson [3] that the position of the posterior electrode bears no important influence on the shape of the chest lead. In fact, the posterior lead can be placed on either arm or leg and the same curve be obtained.

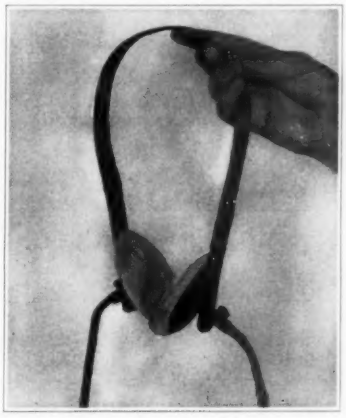

Fig. 1.—New type of chest electrodes with spring clamp to hold in position.

COMMENT

It would be well to mention some of the fundamentals of the theory of electrocardiography in relation to the value of chest leads. The placing of the electrode on the arms and left leg and taking standard leads was by no means an arbitrary matter. Einthoven proposed the scheme of the equilateral triangle for the determination of the real direction of the potential difference in the heart and its manifest value, this being of value only on the frontal plane. The accuracy of the equilateral triangle was proved a short time later by Fahr, who showed that the variation of accuracy was within plus or minus 10 degrees. Wilson also proved this, showing that the galvanometer resistance produced no changes in the measurement of the potential difference.

3. Wilson, F. N.: The Distribution of Potential Produced by the Heart Beat Within the Border and at Its Surface, Am. Heart J. **5**:599 (June) 1930.

At that time, it was mentioned by Fahr [4] that the frontal plane seemed sufficient for all practical purposes. This may still be true. However, there seems to be evidence that in some cases the use of other planes may be of value. Wolferth and Wood [5] demonstrated this in the recognition of abnormal chest leads in cases of coronary thrombosis in which the routine leads showed no abnormal changes.

The application of the equilateral triangle to the anterioposterior or to any plane other than the frontal is not possible. It has been shown by Wilson [6] that any sagittal plane varies with the body to such an extent that no definite geometric figure would bear practical relations as do the arms and leg to the frontal plane of the equilateral triangle.

It is evident that numerous planes present themselves for study. These planes all bear the relation of angle to the frontal plane. As yet, no way has been mentioned in the literature to determine the manifest

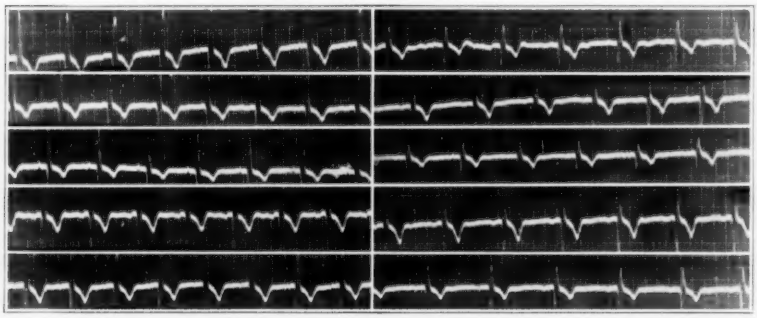

Fig. 2.—Chest leads in two normal subjects in positions A, B, C, D and E from above downward.

value of the potential difference by leads taken in planes other than the frontal. We have chosen several anteroposterior planes from which to take tracings. These were confined to the center and the left side of the chest.

The location of the electrode on the chest is important in securing uniform tracings. The relatively slight changes discernible in the tracings on normal subjects in the various positions become markedly greater in the pathologic subjects, as will be shown. The diminution

4. Fahr, George: An analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920.

5. Wolferth, C. C., and Wood, F. C.: Further Observations on the Use of Chest Lead in the Electrocardiographic Study of Coronary Occlusions, M. Clin. North America **16**:161 (July) 1932. Footnotes 1, 2 and 4.

6. Wilson, F. N.; MacLoed, A. G., and Barker, B. S.: The Potential Variation Produced by the Heart Beat Apices of Einthoven's Triangle, Am. Heart J. **7**:207 (Dec.) 1931.

in amplitude of the Q-R-S complex in position C as compared with the other positions is consistent with the location of the electrode over the base of the heart. This agrees with the fact pointed out by Wilson and Hermann [7] that the electrical effects of that part of the heart nearest the electrode will be exaggerated.

In the tracings from pathologic subjects, we found definite changes in only two positions, namely, positions A and B. Of these, B, over the position of the maximum impulse, was the more common. Because of

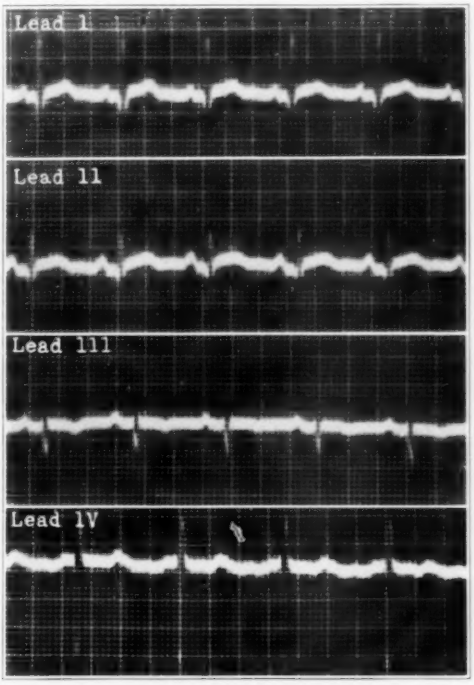

Fig. 3 (case 1).—Chest leads on April 2, 1932.

this, we recommended these two positions for use in cases in which it seems advisable. The possible value in localization of a myocardial infarct by means of change of position or size of electrodes is a problem for postmortem correlation. As yet, there are certain cases in which neither the standard leads nor the chest leads show any change. Our only explanation for this, as yet unproved, is the possible location of a small, infarcted area on the posterior surface of the heart.

7. Wilson, F. N., and Hermann, George: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

REPORT OF PATHOLOGIC CASES

Our series of patients with thrombosis of the coronary artery on whom chest leads were taken falls into three groups: (*a*) those showing normal standard leads and abnormal chest leads, (*b*) those showing abnormal standard as well as abnormal chest leads and (*c*) those showing abnormal standard leads but normal chest leads. A short summary of the clinical findings with the electrocardiographic tracings of these patients follows:

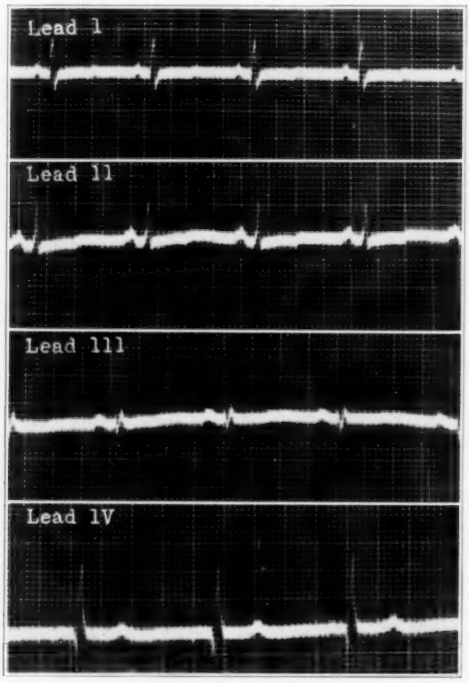

Fig. 4 (case 2).—Chest leads on July 19, 1932.

Cases with Normal Standard Leads and Abnormal Chest Leads.—CASE 1.—W. T. Q., a man, aged 66 years, an executive, entered the hospital on April 1, 1932, forty-eight hours after the onset of severe precordial pain radiating down both arms and accompanied by dyspnea. The temperature was 102 F.; the pulse rate, 110; the blood pressure, 104 systolic and 72 diastolic, and the white blood cells, 8,500. A tracing taken on April 2 (fig. 3) showed practically normal standard leads with a definitely upright T in lead IV taken in position B. In all tracings hereafter, if not otherwise mentioned, lead IV is represented as taken in position B. In all of these instances, the T wave in position A was normal. However, whenever position A revealed an abnormality it was reproduced beneath

position B. Ten days later, April 12, there had developed a definite inversion with the coving of T_1 and T_2 with a high take-off in lead II. In the chest lead, the T wave was iso-electric. On April 27, the findings were essentially the same except for a slightly inverted T in lead IV. On July 23, a diminution in the negativity of T_1 and T_2 was exhibited. On August 8, there was only a slightly inverted T_1 and iso-electric T_2 with the T in lead IV, position B, definitely inverted but not to a normal degree. On September 1, a further progression to normal of the T wave in lead IV was seen.

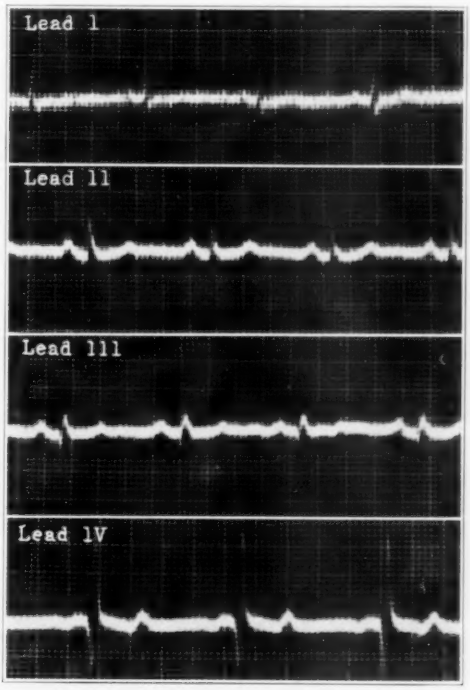

Fig. 5 (case 3).—Chest leads on May 19, 1932.

Owing to lack of space and prohibitive cost of reproduction, only the first tracing of this patient is presented. All subsequent tracings are therefore described in the text only. For the foregoing reasons, in the remainder of the following case reports, only one characteristic abnormal electrocardiograph is reproduced, and the subsequent return to normal is described without reproduction of the tracings.

CASE 2.—M. S., aged 47, a housewife, entered the hospital on May 13, 1932, with the complaint of precordial pressure following exertion attendant on a fright in the mountains eight days previously. The temperature was 99 F.; the pulse rate, 100; the blood pressure, 112 systolic and 70 diastolic, and the whole blood

cells, 10,800. An electrocardiogram taken on admission showed a slightly low take-off and coving with inversion of T_2 and T_3. Four days later, on May 17, there was an upright T_2 and iso-electric T_3. The chest lead, however, revealed a distinctly abnormal upright T wave. This remained the same on May 28, June 11, July 1 and July 19, when the patient was discharged from the hospital improved. The tracing of July 19 is reproduced (fig. 4).

Case 3.—G. B., aged 61, a section foreman, was first seen on Oct. 16, 1930, several days after an attack of severe substernal pain and pressure. This was so

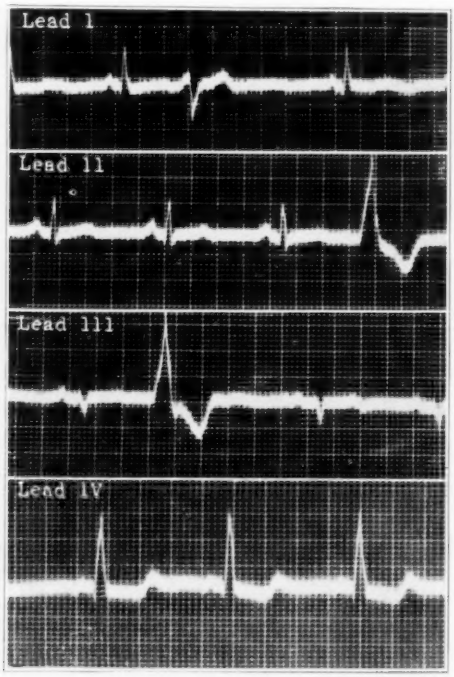

Fig. 6 (case 4).—Chest leads on May 22, 1932.

severe he had to lie down for relief. The pain persisted and radiated down the left arm. The temperature was 100 F.; the pulse rate, 98 and the white blood cells, 10,300. An electrocardiogram at this time revealed a high take-off of T_1 and marked inversion of T_1 and T_2. Recovery was uneventful. He returned on May 19, 1932, with evidence of mild congestive failure, and an electrocardiogram taken on that date (fig. 5) revealed marked slurring of the Q-R-S complex in leads II and III with upright T waves throughout. The chest lead, however, demonstrated a markedly abnormal upright T wave. By June 21, he had developed a complete auricular-ventricular dissociation with a ventricular rate of 50 and also marked slurring of all the Q-R-S complexes. The T wave in lead IV was slightly inverted. On August 30, the complete dissociation had ceased, but a

prolonged P-R interval of 0.24 second was present. The T wave in lead IV in the meantime had become more inverted and was practically normal.

Case 4.—W. B., aged 63 a locomotive engineer, entered the hospital on July 27, 1931, with a story of pain in the anterior portion of the chest radiating down the left arm and brought on by exertion. An electrocardiogram on July 28 showed a practically normal tracing. The patient was discharged with a diagnosis of angina pectoris but reentered the hospital on November 26, after three days of agonizing pain in the chest accompanied by dyspnea. The temperature was 100 F.; the pulse rate, 110; the blood pressure 130 systolic and 86 diastolic, and the white

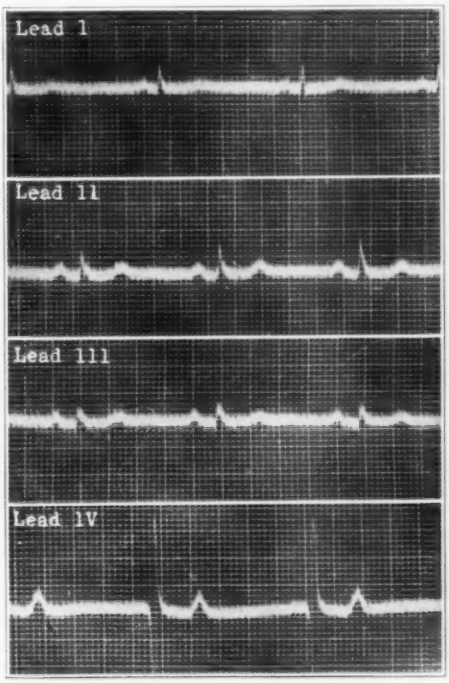

Fig. 7 (case 5).—Chest leads on July 18, 1932.

blood cells, 11,100. An electrocardiogram taken on that date revealed a marked change in T_1 and T_2 which were definitely coved and inverted. On May 22, the patient was recalled for examination, and an electrocardiogram (fig. 6) showed a return to practically normal standard leads with frequent premature ventricular contractions. The first chest lead on this patient taken at this time revealed a markedly abnormal upright T wave, indicating the probable value of the chest lead in demonstrating residual damage months after the standard leads had returned to normal.

Case 5.—W. V., aged 53, a yard clerk, was seen on Nov. 11, 1930, for recurrent attacks of substernal pain with dyspnea and inability to work. The blood

pressure was 150 systolic and 100 diastolic. An electrocardiogram taken then showed low voltage of all Q-R-S complexes with slight slurring of Q-R-S in leads II and III and an iso-electric T_1. On April 18, following an attack clinically simulating coronary thrombosis, an electrocardiograph revealed only slurring of Q-R-S_2 and Q-R-S_3. On May 19, all Q-R-S complexes were slurred, and the T wave in lead IV was abnormal, in that it was of small amplitude although slightly inverted. On July 18 (fig. 7), there was less notching of the Q-R-S complexes, but the T wave in lead IV was markedly upright.

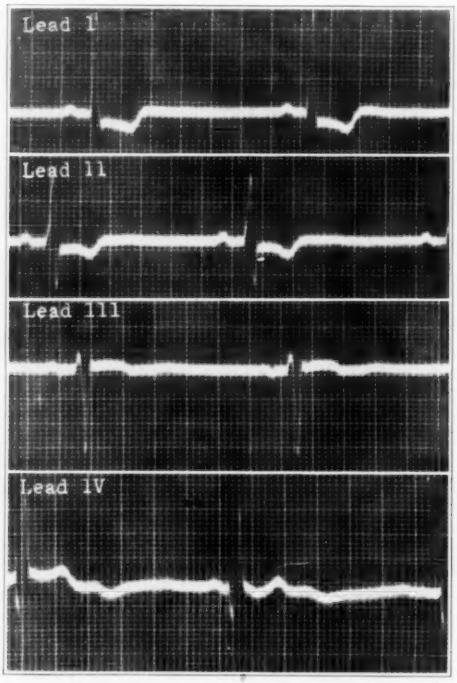

Fig. 8 (case 6).—Chest leads on June 11, 1932.

Coronary Cases with Both Abnormal Standard and Chest Leads.—Case 6.—J. W., aged 57, a section foreman, entered the hospital first on Aug. 4, 1931, following a severe attack of precordial pain lasting eight days. The temperature was 98 F.; the pulse rate, 80; the blood pressure, 234 systolic and 140 diastolic, and the white blood cells, 9,200. An electrocardiogram taken on that date revealed a definite inversion with low take-off of T_1 and T_2 and left ventricular preponderance. The patient was discharged on August 28, but reentered the hospital on May 20, 1932. An electrocardiogram taken the following day revealed T_1 still inverted, but T_2 iso-electric. The T in lead IV was abnormally diphasic. On June 11 (fig. 8), the T wave in lead IV was upright and remained so until the patient's death from uremia on July 17.

Autopsy revealed marked general arteriosclerosis, primary contracted granular kidneys and an old thrombosis of the descending branch of the left coronary artery. A myocardial infarct, 2 by 3 cm., was present on the anterior surface of the left ventricle near the apex directly on the anterior surface of the heart. This patient was the only one in our series of coronary cases who died and on whom we could perform an autopsy to confirm the presence of a coronary thrombosis to correlate with the electrocardiographic changes found in life.

CASE 7.—W. G., aged 63, a railroad conductor, was first seen on May 5, 1932, in the midst of an attack of gripping pain in the chest. This had been present two

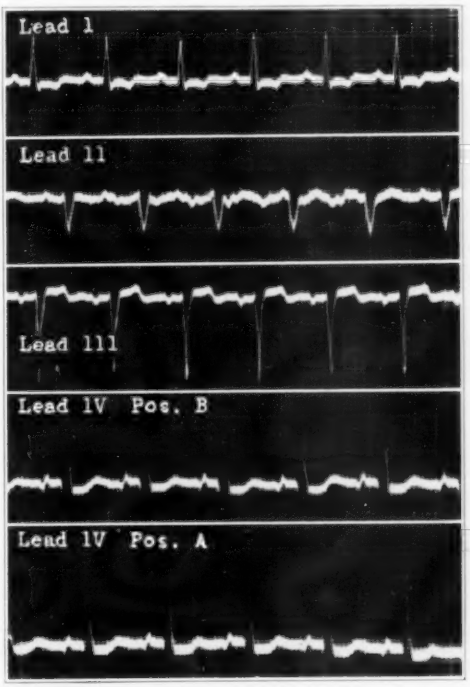

Fig. 9 (case 7).—Chest leads on May 13, 1932.

days. The temperature was 100.4 F.; the pulse rate, 96; the white blood cells, 9,700 and the blood pressure, 136 diastolic and 90 systolic. Evidences of mild congestive failure were present. An electrocardiogram taken on May 7, revealed an upright T wave in lead IV in both positions B and A. The T wave in lead 1 was inverted, and there was moderate spreading of the Q-R-S complexes in all of the three standard leads. On May 13 (fig. 9), the findings were virtually the same. During June and July, the T wave in position A gradually resumed its normal contour, with the T wave in position B becoming first diphasic and then slightly inverted. On August 1 (fig. 10), the T waves in both positions returned to normal and have remained so to date.

Case 8.—H. K., aged 58, an inspector, entered the hospital on May 27, 1932. Fifteen days before admission he had severe knifelike pain over the precordia lasting several hours and radiating down the left arm. He had been dyspneic on slight exertion since. The temperature was 98.6 F.; the pulse rate, 90; the blood pressure, 184 systolic and 100 diastolic, and the white blood cells, 7,100. An electrocardiograph taken on May 28 (fig. 11), revealed an inverted T in lead 1 and abnormal T waves in position A and B of the chest lead. On June 22, a return of the inversion of T_1 to upright and an inversion of T_2 and T_3 was demonstrated. However, in the chest leads in both position, the T waves were

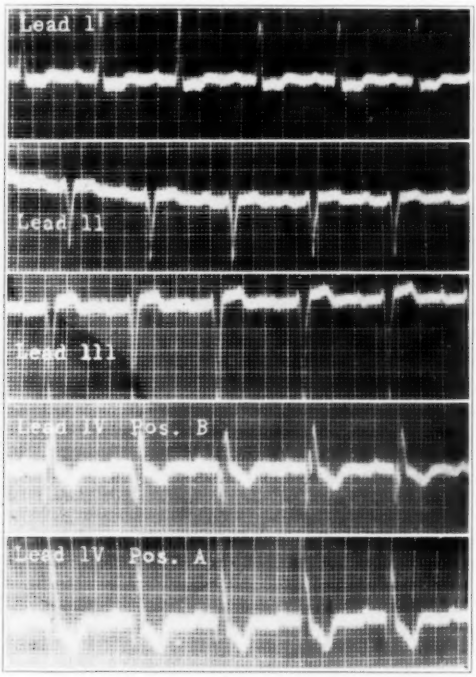

Fig. 10 (case 7).—Chest leads on Aug. 1, 1932.

normal. On September 21, the inversion of T_2 and T_3 had disappeared. The chest lead remained normal.

Case 9.—V. T., aged 34, a rotary worker, entered the hospital on April 25, 1932, following an attack of severe precordial pain lasting one-half day and followed by persistent dyspnea. The temperature was 100.4 F.; the pulse rate, 100; the white blood cells, 14,400, and the blood pressure, 120 systolic and 70 diastolic, and later 110 systolic and 80 diastolic. An electrocardiogram taken on April 30, demonstrated an inversion of T in leads II and III with an only slightly abnormal T in lead IV. The patient was released to his home for convalescence on May 18, and within two days suffered an excruciating pain in the chest which lasted no less than nine days. He required morphine many times

daily for relief. An orthodiagram revealed a marked hypertrophy of the heart. He was seen by several consultants who concurred in the diagnosis of coronary thrombosis. An electrocardiogram taken on May 28, revealed an inverted T_1 with a bigeminy due to frequent nodal extrasystoles. The T wave in lead IV was diphasic. On July 18, the T waves were largely iso-electric, and the T wave in lead IV was upright. Tracings made on August 24 and September 13, demonstrated a gradual return to normal of lead IV. These tracings are not reproduced.

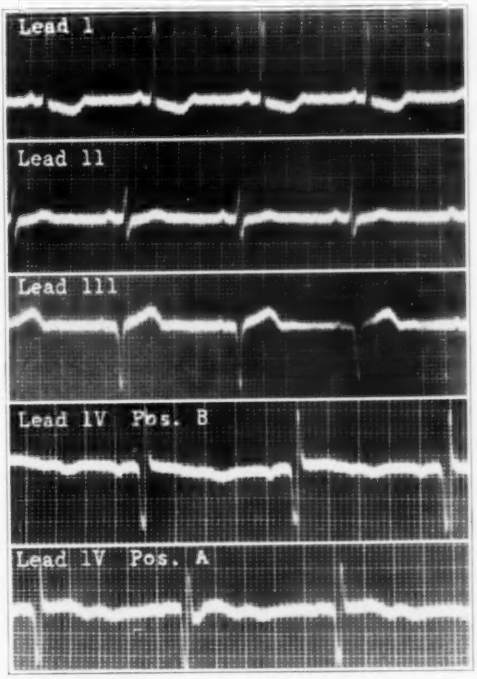

Fig. 11 (case 8).—Chest leads on May 28, 1932.

CASE 10.—W. S., aged 58, a brakeman, was sent into the hospital on Oct. 4, 1932, for re-checking because of a known old hypertension. He had no complaints. Eighteen months prior to admission he had had an attack of precordial pain which lasted several hours and required morphine for relief. There had been no return of pain in the chest, and he stated he was rarely short of breath. The blood pressure was 210 systolic and 100 diastolic. An electrocardiogram, taken on October 8, revealed an inversion of T_1 and T_2 with the T wave in lead IV, position B, diphasic but normal in position A. This tracing is not reproduced.

Coronary Cases with Abnormal Standard Leads and Normal Chest Leads.—CASE 11.—L. R., aged 57, a pumper, entered the hospital on April 25, 1932, with a history of a severe attack of pain in the chest on April 13, lasting eight hours. He was having persistent dyspnea. The temperature was 98.6 F.; the pulse rate,

80, and the white blood cells, 5,200. An electrocardiogram taken on April 28, demonstrated an inverted T_2 and T_3 with left ventricular preponderance. On May 11, these findings still persisted. A chest lead on this date was entirely normal. The patient's dyspnea has persisted. A re-check on the chest lead subsequently showed no change. The tracings are not reproduced as they showed a normal lead IV.

Case 12.—J. W., aged 45 years, a carpenter, was seen on July 7, 1932, following severe substernal pain of agonizing character. Syncope accompanied this distress. The temperature was 100.6 F.; the pulse rate, 110; the white blood cells, 19,000, and

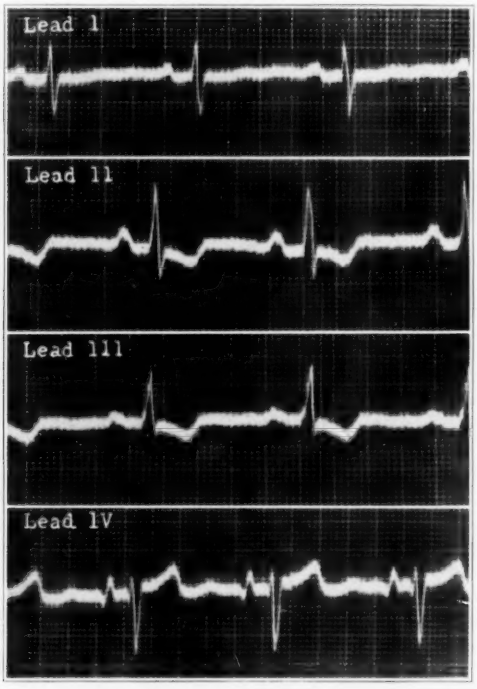

Fig. 12 (case 14).—Chest leads on June 11, 1932.

the blood pressure, 92 systolic and 65 diastolic; later, 104 systolic and 55 diastolic. An electrocardiogram taken on July 9, and one on July 19, revealed a markedly inverted T_2 and T_3 which had a high take-off on the earlier date. The patient was discharged after two months and recalled for a chest lead on May 25. On this date, his T_2 was iso-electric and the T_3 had remained inverted. The T wave in lead IV, however, was normal. These tracings are not reproduced.

Case 13.—H. E., aged 72, a crossing watchman, entered the hospital on Jan. 11, 1930, for prostatic obstruction. The electrocardiograph was normal. The first stage was done on January 17, and the second stage on March 6. The patient was convalescing satisfactorily, when on April 10, while walking in the ward, he

was seized with a terrific precordial pain and fell to the floor. He was in partial shock for some hours. The temperature was 99 F.; the pulse rate, 106; the blood pressure, 96 systolic and 70 diastolic, and the white blood cells, 11,000. A series of three electrocardiograms on April 12, 16 and July 29 revealed progressive changes characteristic of thrombosis of the coronary artery. The patient recovered and has been moderately active since. He was recalled on June 3, 1932, for re-checking; his standard leads revealed a residual marked inversion of T_2 and T_3, but a normal chest lead. His tracings being normal in lead IV, they are not reproduced.

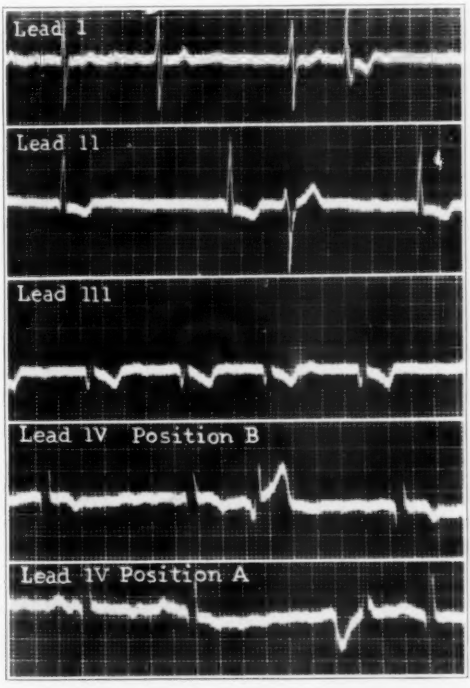

Fig. 13 (case 15).—Chest leads on June 11, 1932.

Chest Leads in Forms of Myocardial Damage other than Coronary Thrombosis.—CASE 14.—J. B., a woman, aged 47, a secretary, had been a known sufferer from rheumatic endocarditis with mitral stenosis for over five years. She had always had a regular sinus rhythm. Her first break in compensation occurred on Nov. 6, 1930. An electrocardiogram taken on that date revealed only a diphasic T_3. On March 3, 1931, an inversion of T_2 and T_3 was present. The patient was fully digitalized at this time. On June 11 (fig. 12), these findings were still present. The T wave in lead IV was highly abnormally upright. The P wave was also upright. These findings were checked on three occasions.

In view of the occasionally reported instances of coronary occlusion in rheumatic pancarditis, we were anxious to check the observations on this patient

post mortem. She died of progressive congestive failure on Sept. 24, 1932. Autopsy by Dr. E. V. Hall of the University of Southern California Medical School demonstrated a contracted, stenosed, "fish mouth" mitral valve. There was no evidence of pericarditis. The coronary arteries were patent throughout. There was no gross area of myocardial fibrosis, although microscopically Aschoff bodies and fibrosis were found.

These findings demonstrate that the T wave changes in lead IV are not solely due to infarction of the myocardium resulting from coronary

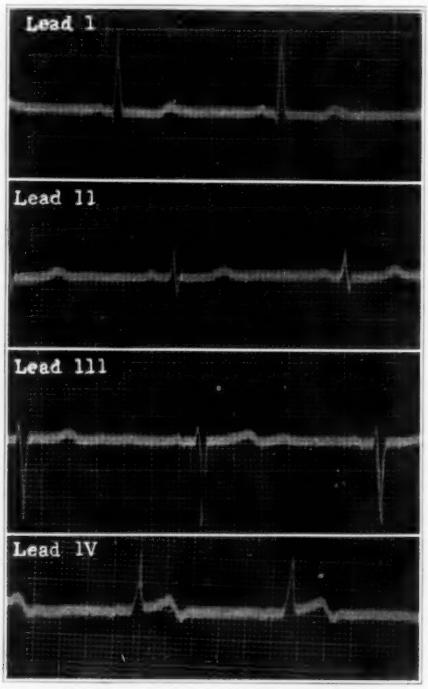

Fig. 14 (case 16).—Chest leads on July 19, 1932.

thrombosis. The character of the inversion of T_2 and T_3 is suggestive of a digitalis effect. However, it is highly unlikely that the T in lead IV can be made upright by digitalis. At least, we have seen no such cases. The patients in cases 1, 2, 3 and 4 all showed upright T in lead IV and received no digitalis whatever.

Case 15.—G. M., aged 36, a laborer, had been followed from 1926 for a rheumatic endocarditis with mitral stenosis and insufficiency. In that time, he had suffered five attacks of decompensation. He maintained a regular sinus rhythm until the onset of an auricular fibrillation early in June, 1932. An electro-

cardiogram taken on Oct. 30, 1929, revealed a diphasic T wave in leads II and III. On May 25, 1932, T_2 and T_3 were inverted. On June 11 (fig. 13), an electrocardiogram revealed the same findings with auricular fibrillation. The chest leads in positions A and B revealed a slightly inverted T in position B and an iso-electric T in position A.

The patient died on October 4, and autopsy revealed a marked mitral stenosis, moderate involvement of the aortic valve and considerable adhesive pericarditis. The coronary arteries were normal. Microscopically, much fibrosis and Aschoff bodies were found.

Case 16.—A. C., aged 45, a laborer, was admitted to the hospital on July 19, 1932, because of swelling of the abdomen and weakness. Examination revealed a markedly enlarged irregular liver, ascites and edema of the legs. The Wassermann reaction was four plus. An orthodiagram revealed a hypertrophied heart and a uniformly widened aortic arch. There were no murmurs. The heart rate was regular. An electrocardiogram taken on July 19 (fig. 14) demonstrated normal standard leads, but an abnormal lead IV with an upright T wave. This was checked on several occasions before death and remained unchanged. The patient died of massive hematemesis on September 24.

Autopsy revealed a primary carcinoma of the liver engrafted on an old cirrhosis of the liver. Advanced syphilitic aortitis was present. The heart was hypertrophied but free from valvular defects, with normal coronary arteries. Microscopically, considerable fibrosis of the myocardium was present.

This was the only patient in our series without coronary disease with a normal electrocardiogram in regard to standard leads and an abnormal chest lead.

We have taken chest leads on six patients with advanced bundle branch block, in all of whom lead IV was normal except for widening of the Q-R-S complex. In a series of several hypertensive patients, all with normal standard electrocardiograms, no abnormalities in the chest leads were discovered. One patient with congenital heart disease presented similar findings. Tracings of these patients are not reproduced.

CONCLUSIONS

From the foregoing study, we feel we are justified in the following conclusions concerning chest leads. By uniform technic, with care as to the position of the electrodes, uniformly normal tracings can be secured on patients with normal hearts. In no instances did we obtain other results, and only in diseased hearts did we obtain abnormal chest leads. The changes found in diseased hearts were not limited to patients with coronary thrombosis. However, they were found most frequently in patients with this affliction. These changes occurred in such patients in whom standard leads were either normal or abnormal. Occasionally apparently the lead IV changes occurred before abnormalities arose in the standard leads. Frequently they reverted to normal before the standard lead abnormalities had done so. In a few instances, they remained for many months presumably as evidence of residual myocardial damage long after the standard leads had become normal.

In a small group with characteristic changes of coronary thrombosis in the standard leads, no abnormalities in the chest lead were noted.

Abnormal chest leads were found in two instances of rheumatic heart disease with mitral stenosis—both with abnormal standard leads—and in one patient with syphilitic heart disease. The latter had normal standard leads. None of these patients had evidence of coronary disease post mortem. One of the rheumatic hearts had considerable adhesive pericarditis.

SUMMARY

1. A standard technic for obtaining chest leads is presented.

2. The position of the electrode on the chest is of importance. Uniform tracings can be secured in normal patients by this technic. In diseased hearts, two positions may show abnormal chest leads. Usually, however, only one of these positions shows such an abnormality. When present in both positions, one may revert to normal earlier than the other.

3. The changes found are not specific for coronary thrombosis, for they were found in other types of myocardial damage confirmed by autopsy.

4. In patients with coronary thrombosis, however, a relatively characteristic chest lead deformity is noticed. Besides Wolferth's and Woods S-T deformity, we found a more frequent abnormality of an iso-electric or upright T wave in lead IV.

5. These T wave abnormalities in the chest lead occasionally precede changes in the standard leads and are, therefore, of value in an earlier confirmation of a diagnosis of coronary thrombosis. They also occur in instances in which the standard leads show the characteristic abnormalities of coronary thrombosis. In some cases of this type, the lead IV changes may be absent.

6. The chest lead abnormalities change with improvement in the patient's condition, implying that an acute underlying process is taking place. Occasionally a return to normal occurs in the chest lead but not in the standard leads. The reverse of this appears to occur even more frequently.

7. As pathologic changes which occur in the myocardium are not all recorded in either the chest leads or the routine leads alone, we feel that it is a worth while procedure to run the chest leads in all cases of suspected or proved myocardial damage. In all the patients on whom we took such tracings, in whom there was clinical evidence of heart disease, either the chest lead or the routine leads showed evidence of myocardial damage. In none of these patients did we find both the routine and the chest leads normal.

Photographs were supplied through the courtesy of Dr. E. L. Shultz and Dale L. Smith, superintendent of the Santa Fe Hospital, and Miss Maureen Springsteen, R. N., gave invaluable technical assistance.

ELECTROCARDIOGRAPHIC STUDIES OF THE DYING HUMAN HEART

WITH OBSERVATIONS ON THE INTRACARDIAC INJECTION OF EPINEPHRINE; REPORT OF TWENTY-FIVE CASES

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Electrocardiography has increased our knowledge of the human heart in health and disease. Its usefulness does not end here, for we may proceed further and investigate the heart in the last moments of life and even after life has apparently ceased. The phenomena of clinical death, as manifested by the cessation of respiration and audible heart sounds, have been observed repeatedly. That cardiac activity does not cease simultaneously with clinical death and that, in certain instances, it continues for a prolonged period is best revealed by the electrocardiograph.

Since the original work of Rhomer[1] in 1911, various observers[2] have described the sequence of events occurring in electrocardiograms taken during the last moments of life. Turner,[3] in a recent review of the literature, collected sixty-five cases in which electrocardiograms

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From the Department of Medicine, Emory University Medical School, and the Emory Division of Grady Hospital.

1. Rhomer: München. med. Wchnschr. **58**:2358, 1911.

2. Robinson, G. C.: A Study with the Electrocardiograph of the Mode of Death of the Human Heart, J. Exper. Med. **16**:291, 1912. Halsey, R. H.: A Case of Ventricular Fibrillation, Heart **6**:67, 1915. Dieuaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrhythmias: Report of Three Cases, Arch. Int. Med. **28**:663 (Nov.) 1921. Schellong, F.: Elektrokardiographische Beobachtungen am sterbenden Menschen, Ztschr. f. d. ges. exper. Med. **36**:297, 1923. Willius, F. A.: Changes in the Mechanism of the Human Heart Preceding and During Death, M. J. & Rec. **119**:49, 1924. Reid, W. D.: Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, Arch. Int. Med. **33**:23 (Jan.) 1924. Kahn, M. H., and Goldstein, I.: The Human Dying Heart, Am. J. M. Sc. **168**:388, 1924. Martini, P., and Sckell, J.: Das Sterben des menschlichen Herzens, Deutsches Arch. f. klin. Med. **158**:350, 1928. Willius, F. A.: Clinical Electrocardiograms, Philadelphia, W. B. Saunders Company, 1929. von Hoesslin, quoted in Berlin letter, J. A. M. A. **96**:786 (March 7) 1931.

3. Turner, K. B.: The Mechanism of Death of the Human Heart as Recorded in the Electrocardiogram, Am. Heart J. **6**:743, 1931.

were taken during death. To this series he added five cases. We are reporting in abstract twenty cases in which electrocardiograms were taken during death, and in detail five other cases in which epinephrine (solution, 1:1,000) was injected into the heart after all deflections in the electrocardiogram had ceased.

In our series an attempt was made to obtain tracings in all three leads during the early events preceding death. After death, events were recorded only in lead II. In most of the cases, complete data were obtained, including the time when the first tracing was taken, the time of clinical death as evidenced by cessation of respiration and audible heart sounds and also the time of occurrence of the last complex in the electrocardiogram. Factors such as age, sex and cause of death were also listed. Finally, the tracings were studied in detail and the

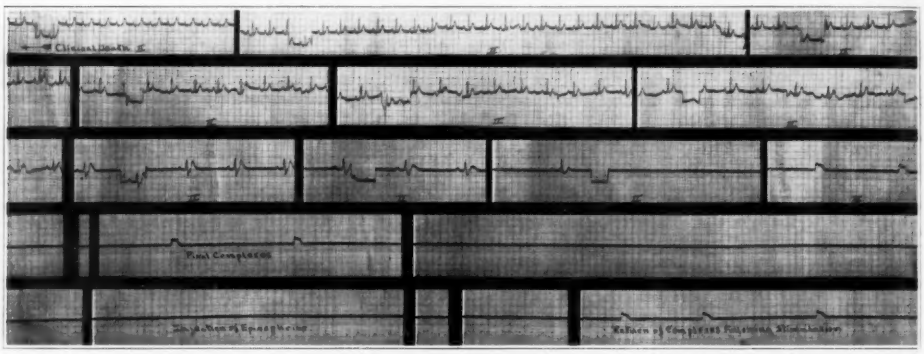

Fig. 1 (case 21).—Sequence of events showing the return of complexes after the injection of epinephrine into the heart.

outstanding features of each tabulated in order of occurrence. The data on the first twenty cases are summarized in the table. The last five cases, in which stimulation was employed, are not included in this group, but are described in detail. The entire group of twenty-five cases is considered in the comment.

REPORT OF SELECTED CASES

CASE 21.—In a woman, aged 22, the cause of death was a gunshot wound of the neck (fig. 1).

Analysis of Electrocardiograms.—Respiration and heart sounds ceased at 7:18 p. m. The record was begun at 7:19 p. m. The final complex occurred at 7:36 p. m. The first electrocardiograms were taken one minute after clinical death. They showed a sinus rhythm with a rate of 100 a minute. The complexes were essentially normal. As events proceeded, the rate gradually decreased and the P-R interval became prolonged. The S wave increased in depth and the high

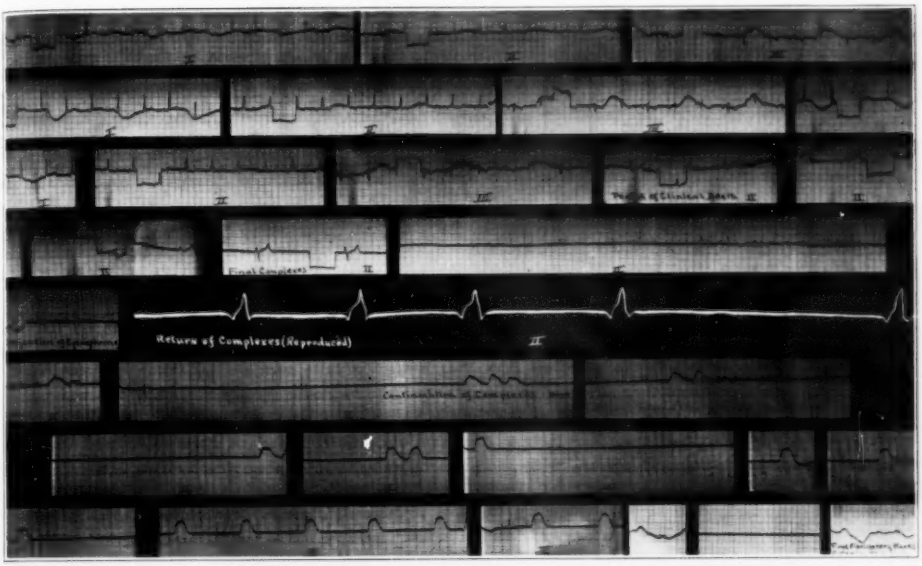

Fig. 2 (case 22).—Sequence of events showing the return of complexes after the injection of epinephrine into the heart.

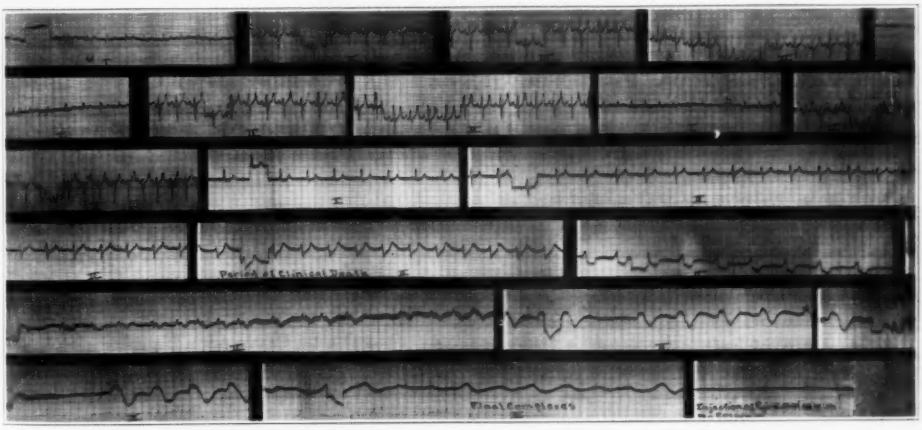

Fig. 3 (case 23).—Sequence of events showing the failure of return of complexes after the injection of epinephrine into the heart.

peaked T wave began below the iso-electric line. The final complexes were low monophasic deflections, apparently ventricular in origin. After a pause of approximately one minute, during which no further complexes occurred, epinephrine was injected into the heart. The site of injection was usually the third left interspace,

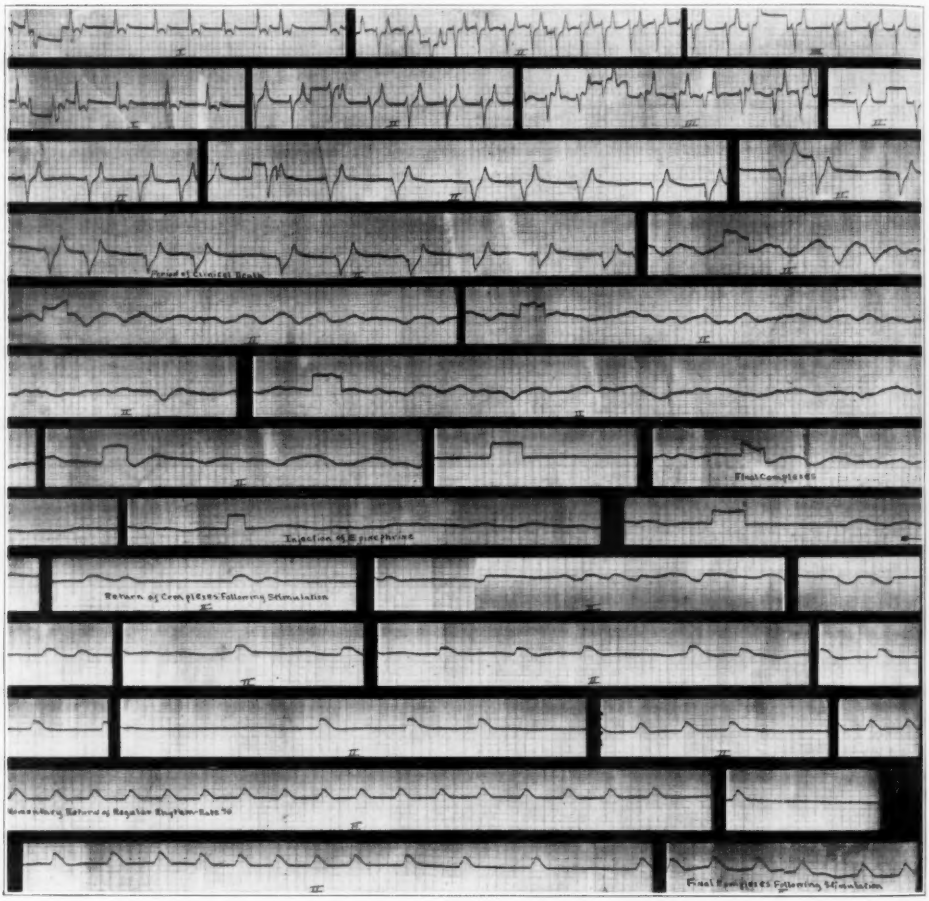

Fig. 4 (case 24).—Sequence of events showing the return of complexes after the injection of epinephrine into the heart.

close to the sternum. Injections were made here because of ease of administration and not with reference to any particular chamber of the heart. A needle measuring about 4 inches (10.1 cm.) in length was used for this purpose, and was inserted until blood flowed back into an attached syringe. Doses of 2, 6 and 5 cc. were injected at intervals of two minutes. Large doses were chosen arbitrarily. Seven minutes after the last injection three monophasic complexes of low amplitude

returned, similar in form to the original final complexes. They began eleven minutes after the original final complex and twenty-nine minutes after clinical death.

CASE 22.—In a woman, aged 44, the cause of death was hypertensive cardiac disease and chronic nephritis (fig. 2).

Analysis of Electrocardiograms.—The record was begun at 8:30 a. m. Respiration and heart sounds ceased at 9:55 a. m. The final complex occurred at 9:56 a. m. The first electrocardiograms were taken one hour and twenty-five minutes before death. They showed an inversion of the P waves in leads II and III, a biphasic T wave in lead II and an inverted T wave in lead III. The rate was 80 a minute. After clinical death the pacemaker became migratory, and varied between the sinus node and the junctional tissues. A slow nodal rhythm supervened and was followed by final complexes which were apparently nodal in origin. After a pause of approximately one minute, during which no further deflections occurred, 5 cc. of epinephrine was injected into the heart. Five complexes, probably nodal in origin, returned. They developed very faintly on a faulty piece of film, and were reproduced as nearly as possible by hand. Injection of epinephrine

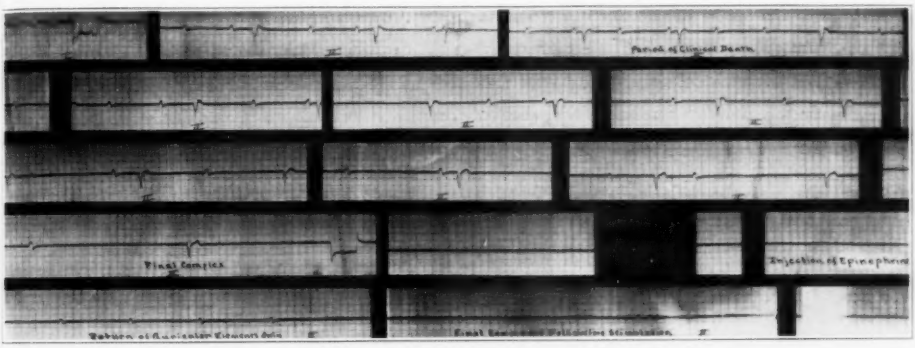

Fig. 5 (case 25).—Sequence of events showing the return of complexes after the injection of epinephrine into the heart.

in 5 cc. quantities was repeated at short intervals and resulted finally in the return of irregularly spaced monophasic complexes. The last injection of epinephrine was given thirty-six minutes after the original final complex and thirty-seven minutes after clinical death. It initiated a series of low fibrillatory waves, apparently ventricular in origin.

CASE 23.—In a man, aged 28, the cause of death was undetermined. The predominant finding was acute pulmonary edema (fig. 3).

Analysis of Electrocardiograms.—The record was begun at 10:48 a. m. Respiration ceased at 1:32 p. m. and the heart sounds at 1:33 p. m. The final complex occurred at 1:35 p. m. The first electrocardiograms were taken two hours and forty-four minutes before death. They showed essentially normal complexes with a tall peaked T wave and a deep S wave in leads II and III. The rate was 110 a minute. There was left ventricular preponderance. The P wave became inverted for a short interval. After clinical death, the rate decreased progressively. No definite P waves occurred. The R waves were of low amplitude and the S waves were deep. The T waves were broad, began below the iso-

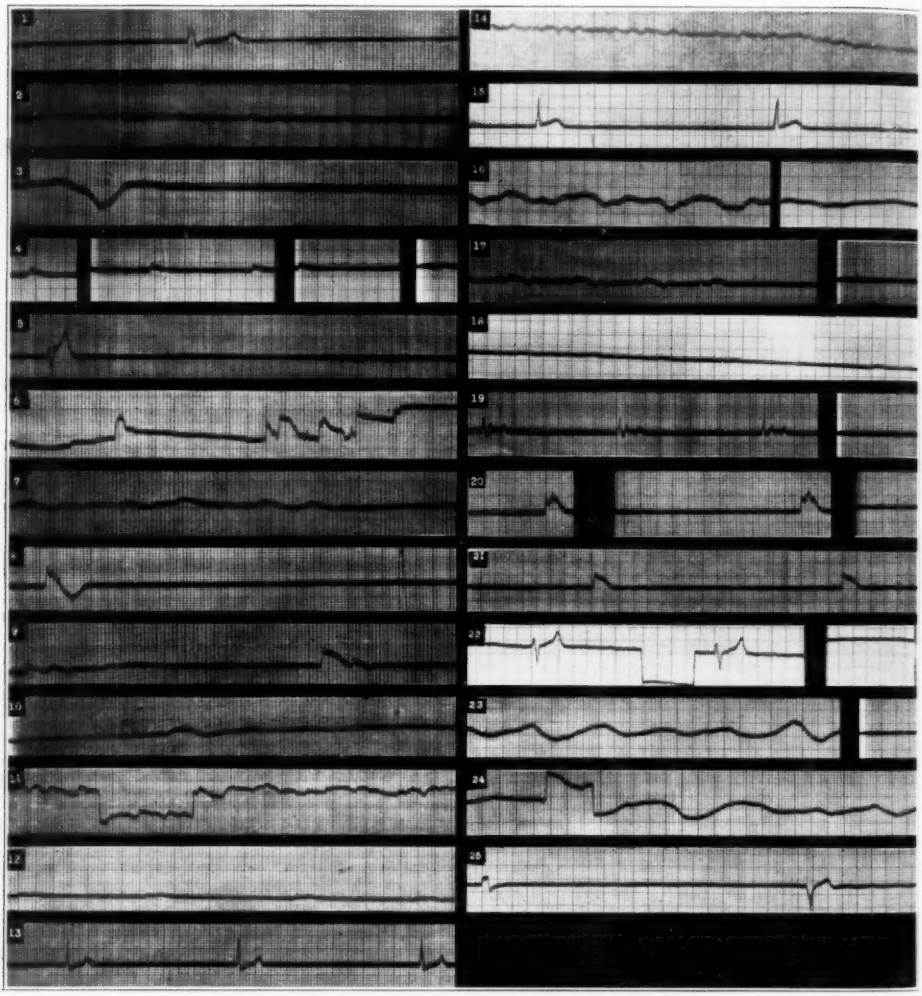

Fig. 6 (cases 1 to 25).—Final complexes: *1*, nodal; *2*, auricular; *3*, ventricular; *4*, ventricular; *5*, ventricular; *6*, ventricular; *7*, ventricular; *8*, ventricular; *9*, ventricular; *10*, ventricular; *11*, ventricular; *12*, auricular; *13*, nodal; *14*, auricular; *15*, nodal; *16*, ventricular; *17*, undetermined; *18*, auricular; *19*, nodal; *20*, ventricular; *21*, ventricular; *22*, nodal; *23*, ventricular; *24*, ventricular, and *25*, nodal.

electric line and finally rose above the R wave. The final complexes were large biphasic deflections, irregularly spaced and ended in low fibrillatory waves, apparently ventricular in origin. Two minutes after the final complex, epinephrine in 5 cc. quantities was injected into the heart at short intervals. There was no response.

CASE 24.—In a man, aged 40, the cause of death was chronic myocardial disease (fig. 4).

Analysis of Electrocardiograms.—The record was begun at 5:08 a. m. Respiration ceased at 5:45 a. m. and the heart sounds at 5:47 a. m. The final complex occurred at 5:49 a. m. The first electrocardiograms were taken thirty-seven minutes before death. They showed a slow nodal rhythm. The rate was 50 a minute. No P waves were seen. The R waves were tall; the T waves began below the iso-electric line and were biphasic. An irregular nodal rhythm of 35 a minute occurred. The Q-R-S interval increased to 0.24 second. After clinical death the complexes changed to low fibrillatory waves, apparently ventricular in origin. After a pause of approximately one minute, 5 cc. of epinephrine was injected into the heart. There was no response. Two minutes later the injection was repeated and resulted in the return of irregularly spaced monophasic complexes. They were followed by other monophasic complexes which, for a brief period, were regularly spaced and occurred at a rate of 75 a minute. These deflections probably arose in the ventricle. They finally became irregularly spaced and assumed the form of those occurring in ventricular fibrillation. They began twenty-seven minutes after the original final complex and thirty-one minutes after clinical death.

CASE 25.—In a woman, aged 45, the cause of death was chronic myocardial disease (fig. 5).

Analysis of Electrocardiograms.—The record was begun at 3:22 p. m. Respiration ceased at 3:27 p. m. and the heart sounds at 3:30 p. m. The final complex occurred at 3:33 p. m. The first electrocardiograms were taken five minutes before death. The rate was 90 and the complexes were essentially normal in lead I. Partial heart block occurred. The subsequent complexes were irregularly spaced and consisted of broad, high, notched P waves, followed by ventricular complexes of two types. One type consisted of a tall R wave, a deep S wave with notching on the upstroke and a T wave which originated above the iso-electric line and was poorly formed. The other type was of more normal appearance and consisted of a tall R wave, a deep S wave and an upright T wave which was rounded and began below the iso-electric line. The final complex was probably nodal in origin and was essentially normal in form. After a pause of approximately one minute, during which no deflections occurred, 2 cc. of epinephrine was injected into the heart. The injections were repeated at intervals of one minute for two additional doses without response. Three minutes after the original injection, 2 cc. of epinephrine resulted in a return of complexes. They consisted of auricular elements only and were low, broad and notched. The final auricular complex, following stimulation, began five minutes after the original final complex and twelve minutes after clinical death.

COMMENT

The findings in our cases differ in no marked degree from those reported by previous observers, except for the last five cases in which epinephrine was injected into the heart. We know of only one previous report of the electrocardiographic findings in attempts to resusci-

Summary of Principal Events in Cases 1 to 20

Case	Sex	Age	Cause of Death	Time Elements: Record Began	Time Elements: Respiration Ceased	Time Elements: Heart Sounds Ceased	Time Elements: Final Complex	Origin Final Complex	Sequence of Events in Electrocardiogram
1	M	..	Chronic nephritis	.....	.....	.....	.....	A-V node*	Auricular extrasystole; nodal rhythm with retrograde conduction; absent P waves; periods of auricular and ventricular asystole; final nodal standstill
2	M	14	Abscess of brain	7:40 p. m.	.....	.....	7:55 p. m.	Auricle	Sinus tachycardia; partial heart block; ventricular asystole; fibrillatory waves of auricle; final auricular standstill
3	M	30	Pulmonary tuberculosis	6:30 a. m.	.....	.....	6:45 a. m.	Ventricle	Nodal rhythm; decreased rate; idioventricular conduction defect; final ventricular standstill
4	M	25	Lobar pneumonia	10:25 a. m.	3:21 p. m.	.....	3:24 p. m.	Ventricle	Sinus tachycardia; ventricular tachycardia; ventricular fibrillation; final ventricular standstill
5	F	55	Cerebral hemorrhage	1:10 a. m.	1:59 a. m.	.....	2:03 a. m.	Ventricle	Sinus tachycardia; irregular nodal rhythm; migratory pacemaker; ventricular extrasystole; final ventricular standstill
6	M	28	Pneumococcic meningitis	9:49 p. m.	9:50 p. m.	.....	9:54 p. m.	Ventricle	Sinus tachycardia; ventricular extrasystole; partial heart block; ventricular asystole; complete heart block; auricular and ventricular asystole; ventricular fibrillation; final ventricular standstill
7	F	49	Lobar pneumonia	2/6/31 3:00 p. m.	2/7/31 2:40 p. m.	.....	.....	Ventricle	Normal tracing; ventricular extrasystole; nodal rhythm; ventricular tachycardia; ventricular fibrillation; final ventricular standstill
8	F	30	Septicemia	.....	6:40 p. m.	.....	.....	Ventricle	Sinus tachycardia; nodal rhythm; idioventricular conduction defect; auricular and ventricular asystole; final ventricular standstill
9	F	18	Streptococcic meningitis	11:05 p. m.	11:05 p. m.	11:05 p. m.	11:40 p. m.	Ventricle	Normal tracing, lead I; ventricular fibrillation; recovery; ventricular fibrillation; recovery; auricular and ventricular asystole; ventricular fibrillation; auricular and ventricular asystole; ventricular fibrillation; final ventricular standstill
10	M	35	Unknown	9:00 a. m.	9:40 a. m.	9:40 a. m.	9:43 a. m.	Ventricle	Normal tracing; nodal rhythm; absence of P waves; return of P waves; nodal rhythm; ventricular tachycardia; ventricular fibrillation; final ventricular standstill
11	F	20	Miliary tuberculosis	5:00 p. m.	9:55 p. m.	9:55 p. m.	9:57 p. m.	Ventricle	Sinus tachycardia; nodal rhythm; ventricular tachycardia; ventricular fibrillation; final ventricular standstill

Summary of Principal Events of Cases 1 to 20—Continued

Case	Sex	Age	Cause of Death	Time Elements: Record Began	Respiration Ceased	Heart Sounds Ceased	Final Complex	Origin Final Complex	Sequence of Events in Electrocardiogram
12	M	..	Fractured skull	11:09 p. m.	11:20 p. m.	11:20 p. m.	11:24 p. m.	Auricle	Normal tracing; ventricular escape; ventricular asystole; ventricular tachycardia; final auricular standstill
13	F	..	Intestinal obstruction	7:15 a. m.	8:10 a. m.	8:10 a. m.	8:13 a. m.	A-V node*	Sinus tachycardia; normal rhythm; nodal rhythm; final nodal standstill
14	F	32	Septicemia	9:00 a. m.	12:00 noon	11:58 a. m.	12:06 p. m.	Auricle	Sinus tachycardia; idioventricular conduction defect; terminal fibrillatory waves; probably auricular in origin; final auricular standstill
15	M	43	Rupture of aneurysm	9:32 a. m.	9:36 a. m.	9:38 a. m.	9:43 a. m.	A-V node*	Nodal rhythm; sinus rhythm; auricular and ventricular asystole; nodal rhythm; sinus rhythm; partial heart block; nodal rhythm; final nodal standstill
16	M	40	Lobar pneumonia	11:37 a. m.	11:38 a. m.	11:39 a. m.	11:41 a. m.	Ventricle	Nodal rhythm; ventricular fibrillation; auricular and ventricular asystole; ventricular fibrillation; final ventricular standstill
17	F	30	Chronic myocardiac disease	3/5/31 5:00 p. m.	3/6/31 12:25 a. m.	12:25 a. m.	12:28 a. m.	Undetermined	Sinus tachycardia; partial heart block; sino-auricular block; nodal extrasystole; nodal rhythm; final complexes with auricular and ventricular elements
18	M	22	Lobar pneumonia	11:06 a. m.	11:27 a. m.	11:28 a. m.	11:31 a. m.	Auricle	Sinus tachycardia; nodal rhythm; migratory pacemaker; nodal extrasystole; partial heart block; ventricular asystole; final auricular standstill
19	F	47	Hypernephroma	6:20 a. m.	6:33 a. m.	6:33 a. m.	6:36 a. m.	A-V node*	Sinus tachycardia; changing form of „P" wave; sino-auricular block; nodal rhythm with retrograde conduction; final nodal standstill
20	M	30	Lobar pneumonia	4:00 p. m.	6:32 p. m.	6:36 p. m.	6:42 p. m.	Ventricle	Sinus tachycardia; nodal rhythm; idioventricular conduction defect; final ventricular standstill

* Auriculoventricular node.

tate the dying human heart with intracardiac injections of epinephrine. Levine and Matton [4] reported a case of the Adams-Stokes syndrome in which ventricular fibrillation occurred for a period of three and a half minutes and was followed by ventricular standstill for seventy-nine seconds. The rhythm returned to normal after the intracardiac injection of 0.5 cc. of epinephrine hydrochloride (solution, 1:1,000).

4. Levine, S. A., and Matton, Marcel: Observations on a Case of Adams-Stokes Syndrome, Showing Ventricular Fibrillation and Asystole Lasting Five Minutes With Recovery Following the Intracardiac Injection of Adrenalin, Heart **12**:271, 1926.

The patient was able finally to leave the hospital, but died a short time later, presumably from a similar attack. This case differs from those which we report in that P waves continued to occur in the electrocardiograms after death, whereas in our cases there was standstill of both auricles and ventricles before stimulation was employed. Levine's and Matton's patient lived, whereas we were unable to restore our patients to life after complete cardiac standstill.

In our series, there were thirteen male and twelve female patients (table). The causes of death varied. The age limits ranged from 14 to 55 years. The period elapsing from clinical death to the final complex averaged five minutes. The longest individual period was thirty-five minutes.

A consideration of the arrhythmias occurring during the sequence of events is interesting. Heart block in some form occurred in seven cases. Sino-auricular block occurred twice. Premature contractions occurred in ten cases, being of auricular origin in one case, nodal in four cases and ventricular in five cases. Auricular fibrillation did not occur definitely. Ventricular fibrillation occurred in ten cases. In two cases there were temporary periods of recovery from fibrillation, and in one case there were four distinct periods of fibrillation. It was the terminal event in cessation of cardiac activity in nine of the twenty-five cases. Nodal rhythm was quite common and occurred in sixteen cases. Periods of asystole of either auricle or ventricle or both occurred in ten cases. The average asystolic period was from ten to fifteen seconds, while the longest period was thirty-five seconds. Complexes resembling ventricular tachycardia occurred in four cases. Intraventricular conduction defects occurred in five cases.

The site of origin of final complexes varied (fig. 6). It is difficult in the short tracings shown to judge the site of origin of the final complexes. Interpretation was based, in some instances, on preceding tracings, and therefore may not be obvious from the tracings reproduced here. As near as could be determined, the final complex, before stimulation, arose in the ventricle in fourteen cases, at the auriculoventricular node in six cases and in the auricle in four cases, and it was undetermined in one case. The final complex after stimulation in the last five cases differed from the original final complex in two cases. In case 22, ventricular fibrillation, which had not been present before stimulation, occurred as a terminal event after stimulation. In case 25, the final complex after stimulation was auricular in origin, whereas before stimulation it had been nodal in origin.

The usual sequence of events was that the tracings began with sinus tachycardia, which was followed by progressive slowing of the rate. Usually a slow nodal rhythm followed clinical death. A large number

of tracings manifested variations in the irritability of the sinus node. The pacemaker was frequently migratory in type, and shifted between the sinus node and the auriculoventricular node. Short periods of asystole occurred frequently. Heart block and extrasystoles were the common arrhythmias. Ventricular fibrillation was a frequent terminal event, preceding standstill of the heart.

The last five cases of our series are worthy of special consideration. In four cases we were able to cause a return of complexes with epinephrine after standstill of both auricles and ventricles. The electrocardiograms of case 24 (fig. 4) are of particular interest. They show a momentary return of a regular rhythm with monophasic complexes, probably of ventricular origin. Each complex seems to be formed by a fusion of the R and T waves. These complexes finally become irregularly spaced and are converted into waves, interpreted as those of ventricular fibrillation.

Hyman,[5] in a recent review of the literature on resuscitation of the stopped heart by intracardiac therapy, concluded that stimulation may be applied most effectively to the right auricle because the impulse for contraction originates there. He thought that stimulation of the ventricle might lead to ventricular fibrillation, which is incompatible with life. The reverse would not be true necessarily, should the auricles fibrillate. Injections into the heart muscle were considered to be more effective than those made into the cavities of the heart or the pericardium. The response of the heart was not considered to be specific for any pharmacodynamic action, as a wide variety of drugs had been used for injection. The success of intracardiac therapy seemed to depend more on the irritant effect of puncturing the heart muscle with the injecting needle than on the substance injected. Hyman considered that the work of Meyer[6] and others suggested that all hearts in which cardiac arrest had occurred could be divided into two groups. In group 1 was placed the healthy asystolic heart that stops under narcosis, anesthesia, shock, accident, injury and collapse, while in group 2 may be placed the pathologic heart suffering from the effects of acute and chronic disease with resulting myocardiac degeneration and general vasomotor breakdown. A review of successful cases indicated that intracardiac therapy should be most effective in group 1, while failure would most likely occur in group 2.

Interpretation of our results is a difficult task. The investigations of Hyman suggest that in our case 21, injections were possibly made

5. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch. Int. Med. **46**:553 (Oct.) 1930.

6. Meyer, C.: Jahrb. f. Kinderh. **107**:76, 1924.

into the ventricle and resulted in the return of ventricular deflections. Possibly this happened also in cases 22 and 24, and resulted in the onset of ventricular fibrillation. In case 25, the injecting needle may have reached the auricle, as the returning deflections were auricular in type. Since four of our five patients belonged to group 2, in which resuscitation of the heart is not to be expected, our lack of success may be partially explained. Other factors should be considered, however. The large doses of epinephrine used may have had a damaging effect on the myocardium. The effect of anoxemia on the heart muscle and the vital brain centers, controlling respiration and vasomotor activity, should be considered. When the heart muscle and these vital centers have not been deprived of oxygen too long, resuscitation may occur, but if the period of asphyxia has been prolonged, resuscitation is improbable because of the fatal effects of the anoxemia.

The significance of complexes occurring in electrocardiograms taken after clinical death is unexplained. Whether these complexes are an indication of contraction of the heart muscle or whether they represent the spread of an excitation wave without muscular contraction is undetermined. If these complexes which may occur for long periods are an indication of contraction of the heart muscle after death, it is possible that they exert sufficient pressure on the aortic leaflets to permit a sufficient flow of blood in the cerebral and coronary arteries to maintain life for a brief period of time. This would tend to explain the clinical reports of patients being revived as long as thirty minutes after apparent death. In our cases, in which stimulation was delayed until all cardiac contractions had ceased and no further complexes occurred, the nutrition of the brain and heart muscle was probably impaired to such an extent that resuscitation was not possible, even though a few feeble contractions followed the injection of epinephrine into the heart.

The demonstration of the response of the heart muscle to intracardiac therapy, after prolonged asphyxia, increases interest in the problem of cardiac resuscitation. Further investigations are needed to determine the significance of contractions of the heart muscle after death, with the possibility of cerebral and coronary flow. It is obvious that investigations of this type are best adapted to animal experimentation.

SUMMARY

1. Twenty-five cases are reported in which electrocardiograms were taken during death. This series makes a total of ninety-five reported cases.

2. Our series is analyzed briefly with regard to age, arrhythmias, sequence of events and final complexes.

3. The last five cases are described in detail and show the effect of injecting epinephrine into the heart after all contractions had ceased and the heart was at a complete standstill. In four cases, electrocardiograms showed that complexes returned following stimulation.

4. The demonstration of the response of the heart muscle to stimulation after prolonged asphyxia increases interest in the problem of cardiac resuscitation.

DIFFUSE AMYLOIDOSIS

THREE UNUSUAL CASES: A CLINICAL AND PATHOLOGIC STUDY

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The occurrence of diffuse amyloidosis among patients suffering from chronic sepsis, tuberculosis, syphilis and certain malignant diseases has long been recognized, and it should be suspected in the presence of these conditions if hepatic or splenic enlargement or evidences of renal involvement are noted.

In the absence of disease ordinarily bearing an etiologic relationship to amyloidosis, however, this condition probably often escapes recognition because it is not suspected. Atypical cases of amyloidosis which may be of obscure origin do occur. Three unusual cases of diffuse amyloidosis are herewith presented. Case 1 has been reported previously,[1] and we are including only an abstract of it.

REPORT OF CASES

CASE 1.—*History.*—A Mexican, aged 38, was admitted to the Mayo Clinic on Jan. 28, 1929, at which time a diagnosis of lymphosarcoma of Hodgkin's type was made. This was confirmed by histologic studies of one of the enlarged cervical nodes. Roentgen treatment was given, and because of the vague abdominal symptoms and because the patient's apparent illness was somewhat out of proportion to the amount of objective evidence of Hodgkin's disease, the entire neck, thorax, abdomen and back were irradiated. The response to treatment by roentgen rays was striking.

Examination.—The patient returned for examination on May 29. His condition was still much improved, but because he was complaining of thoracic pain, and because of the slight residual cervical adenopathy on the left and a questionable small, tender mass deep in the epigastrium, he was again given intensive treatment by roentgen rays, and again his condition improved promptly. He was readmitted to the clinic on December 12, but this time he presented an entirely different appearance. No evidence of the previous Hodgkin's disease was demontrable, but he had lost weight and was weak and toxemic, although not appreciably anemic or cachectic. On both previous admissions his cardiorenal-vascular

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From the Division of Medicine and the Section on Pathologic Anatomy, the Mayo Clinic.

1. Bannick, E. G., and Nelson, W. B.: Diffuse Amyloidosis of Unknown Etiology, M. Clin. North America **14**:773 (Nov.) 1930.

status had apparently been entirely normal, but this time urinalysis disclosed severe albuminuria, mild hematuria and a few hyaline and waxy casts. The specific gravity of the urine, in spite of the severe albuminuria, was only 1.015. The blood pressure in millimeters of mercury was 100 systolic and 70 diastolic. Excretion of phenolsulphonphthalein was 15 per cent in one hour. The value for blood urea was 58 mg. for each hundred cubic centimeters. The concentration of hemoglobin was 75 per cent; erythrocytes numbered 4,360,000 and leukocytes 8,100 in each cubic millimeter of blood. The differential leukocyte count was essentially normal. There were 3.8 Gm. of serum protein for each hundred cubic centimeters, of which 27 per cent was albumin. The value for blood cholesterol was 235 mg. for each hundred cubic centimeters.

Because of the unusual renal picture the possibility of amyloid disease was considered and will be commented on later. A congo red test was strikingly positive. More than 75 per cent of the congo red that was injected intravenously (18 cc. of a 1.5 per cent solution) had disappeared from the blood stream at the end of an hour; practically no dye was demonstrable in the urine at the end of an hour and very little in five hours. This made the diagnosis of amyloidosis likely, and although the liver was not perceptibly enlarged, there was marked retention of bromsulphalein, indicating extensive involvement of this organ.

Course of Illness.—In spite of attempts at treatment, the patient failed rapidly and died on the twelfth day after admission. At the end he resembled a patient in a crisis of Addison's disease, with vomiting, extreme restlessness, falling blood pressure, and weak cardiac sounds. The value for blood urea on the day before death was 56 mg. for each hundred cubic centimeters. A diagnosis was made of diffuse amyloidosis with renal and hepatic insufficiency and a possibility of suprarenal insufficiency

Necropsy.—The complete records of necropsy, including photomicrographs of a section of the kidney, were given in the original report. The final anatomic diagnosis was: (1) lymphosarcoma (Hodgkin's type) of the prevertebral and pancreatic lymph nodes and liver (small nodule); (2) amyloidosis of the spleen, kidneys, liver, suprarenal glands, ileum and colon; (3) healed duodenal ulcer, and (4) pseudomembranous enterocolitis.

Case 2.—*History.*—A man, aged 44, was admitted to the clinic on Dec. 13, 1931. In the two years previous to his admission he had been troubled with indigestion, the symptoms of which were sour stomach, a sense of fulness, some pain and distress after meals and considerable bloating. These symptoms followed ingestion of any type of food. At certain times, however, he was able to eat without distress. Six months before his admission the symptoms of indigestion had become considerably exaggerated, and on examination the liver had been found to be enlarged. At that time he entered a hospital for examination, and in the course of his stay he had begun to vomit following meals and to fail in strength. A diagnosis of cirrhosis of the liver had been made, although the question of Hodgkin's disease had been raised because of some enlargement of the inguinal and axillary nodes and because he had been annoyed by considerable pruritus without jaundice.

In October, 1931, two and a half months before the patient's admission to the clinic, surgical exploration had been carried out. The report stated that the liver was smooth, did not look cirrhotic grossly, and yet was definitely enlarged and abnormal. Biopsy of a specimen from the liver had disclosed some changes that were difficult to interpret, but which suggested chronic hepatitis. The gallbladder, although appearing normal, was drained. Convalescence from the surgical procedure had been slow. During the first few days of ambulatory convalescence, the abdomen had gradually become enlarged. Shortly after this, the patient had

experienced abdominal pains, more severe than at any time previously, and at that time the possibility of appendicitis was considered, but the attack was atypical and operation was deferred. Following this attack, the genitalia had been edematous, and then edema of the lower extremities had occurred for the first time. Finally, general anasarca had developed. Before he came to the clinic the patient had received two intravenous injections of merbaphen, one of which had produced slight diuresis, and the other, diarrhea.

Examination.—At the time of the patient's admission to the clinic, he was complaining chiefly of bloating and a sensation of abdominal pressure. He was weak, and he walked with much difficulty. He appeared to be very ill and somewhat anemic. The abdomen was tense with ascites. The liver was large and very firm. The blood pressure was 90 systolic and 55 diastolic. Neurologic examination disclosed generalized decrease in activity of all deep reflexes and positive bilateral Babinski and Hoffmann signs. There was dysarthria, with slurring speech. It was felt that from a neurologic standpoint there was no definite evidence to indicate syphilis or to aid in the diagnosis. Albuminuria was graded 2 to 3. Erythrocytes in the urine were graded 1 to 2, and there was an occasional pus cell and some hyaline casts. Excretion of phenolsulphonphthalein varied from 15 to 25 per cent in one hour and fifteen minutes. Erythrocytes numbered about 4,000,000 and leukocytes 10,200 in each cubic millimeter of blood. The value for urea was 58 mg. in each hundred cubic centimeters of blood; the carbon dioxide-combining power of the plasma and the value for plasma chlorides were normal. On a test of hepatic function, retention of bromsulphalein was graded 1, but the response to the galactose tolerance test was normal. The value for bilirubin was 1.5 mg. in each hundred cubic centimeters of serum, and the van den Bergh reaction was indirect. The basal metabolic rate was —18. The ocular fundi were normal. During the twenty-eight days that the patient was under observation his pulse rate was normal and his temperature definitely subnormal.

Operation and Course.—On the eighteenth day after the patient's admission, abdominal paracentesis was done, 2,000 cc. of straw-colored fluid being removed. Microscopic study of this fluid disclosed that most of the cells were leukocytes. The course of the illness was progressively downward almost from the date of admission to the clinic. About a week after admission slight jaundice developed. This became progressively more pronounced, so that the value for bilirubin rose to 9.4 mg. for each hundred cubic centimeters of serum, and the van den Bergh reaction became direct.

There was a steady rise in the value for blood urea until it reached 549 mg. shortly before death. Analysis of the urine daily disclosed persistently marked albuminuria, for the most part graded 3, and presence of erythrocytes was graded 1 to 2. Throughout this period marked hypotension was a feature of note. Most of the time the blood pressure was about 65 systolic and 40 diastolic, and readings as low as 55 systolic and 40 diastolic were obtained. This suggested suprarenal insufficiency, and the manner of the patient's decline simulated that which occurs in the terminal crisis of Addison's disease. Finally, there developed hiccup, diarrhea, delirium and coma, and the patient died twenty-eight days after admission. During the last days of his life, he manifested a combination of profound renal, suprarenal and hepatic insufficiency, the cause of which remained undetermined. Necropsy was performed three hours after death.

Necropsy.—Icterus, graded 2, was present. The peritoneal cavity contained 3,000 cc. of clear yellow fluid. The pleural cavities contained clear yellow fluid, there being 800 cc. in the right and 300 cc. in the left. The heart weighed 379 Gm. The

consistence of the muscle was increased. It was friable and waxlike. The lungs were edematous and congested. The spleen weighed 500 Gm. It was slate gray, with reddish mottling. The consistence was increased. The normal splenic markings were obscured and the surface was waxy. The application of iodine revealed a rapidly developing change from dark brown to almost black. The typical reddish-brown hue, which usually characterizes amyloid deposits, did not appear. The liver weighed 3,187 Gm. The capsule was smooth. The color was brownish red, and the consistence was increased. The sectioned surface was waxy in appearance. The lobular markings were poorly shown. The accessory portal veins were of increased prominence. The veins in the lower portion of the esophagus were also dilated. The lymph nodes about the head and body of the pancreas were slightly enlarged and firm. The left kidney weighed 174 Gm., and the right, 180 Gm. The cortical surfaces appeared somewhat granular. Their consistence was slightly increased. Iodine tests were applied to the cardiac muscle, liver, suprarenal glands and kidneys, with a response similar to that described for the spleen. The muscle cells of the myocardium, when examined microscopically,[2] revealed marked atrophy. The stroma was increased because of narrow bands of hyaline deposits. In some areas wide zones were seen where muscle cells had entirely disappeared. In the sections stained with congo red this hyaline intercellular substance had a marked affinity for the dye. The walls of some pulmonary alveoli and of many blood vessels contained acellular deposits of hyaline material which stained bright red with congo red. The normal structure of the spleen was transformed by diffuse deposition of hyaline substance. The distinctive malpighian corpuscles were entirely gone, as well as practically all other pulp and stroma cells. The sinusoidal spaces were greatly decreased in number, and between surviving spaces, hyaline, eosin-staining deposits appeared (fig. 1*A*). With congo red the sections were stained diffusely red, with the exception of the nuclei and cytoplasm of cells. Methyl violet gave the characteristic amyloid reaction, but not so consistently as sections stained with congo red. Iodine alone or iodine and sulphuric acid failed to elicit a typical amyloid reaction in several trials. Sections taken from all lobes of the liver revealed extensive atrophy of the hepatic cords, between which was an accumulation of hyaline substance beneath the sinusoidal membrane (fig. 1*B*). Bile thrombi were present in the centers of the lobules. The hyaline substance was most clearly demonstrated by staining with congo red. With methyl violet, the reaction was suggestive of amyloid, but not so well revealed. Iodine alone or iodine and sulphuric acid failed to produce typical reactions. In the walls of the blood vessels and connective tissue of the stomach and duodenum, deposits of hyaline material gave a positive reaction with congo red. In the pancreas there was considerable hyaline transformation in the walls of blood vessels, in the interstitial connective tissue and, to some extent, focally about the pancreatic acini and in the islands of Langerhans. Staining with congo red made the change more evident. Sections of the kidneys revealed that all of the glomeruli were involved to some degree by isolated hyaline masses seen beneath the capillary basement membranes (fig. 2*A*). Similar changes also were found in the walls of arteries throughout both the cortex and the medulla and also in the intertubular stroma. Subcapsular zones of the cortex revealed, in

2. The tissues in case 2 and 3 were fixed in Orth's fluid, from which paraffin sections were prepared. These sections were stained with both hematoxylin-eosin and with congo red. Routine descriptions were of sections stained with hematoxylin-eosin, supplemented by descriptions of sections stained with congo red. Frozen sections of tissues fixed in formaldehyde were also made and stained with methyl violet and iodine.

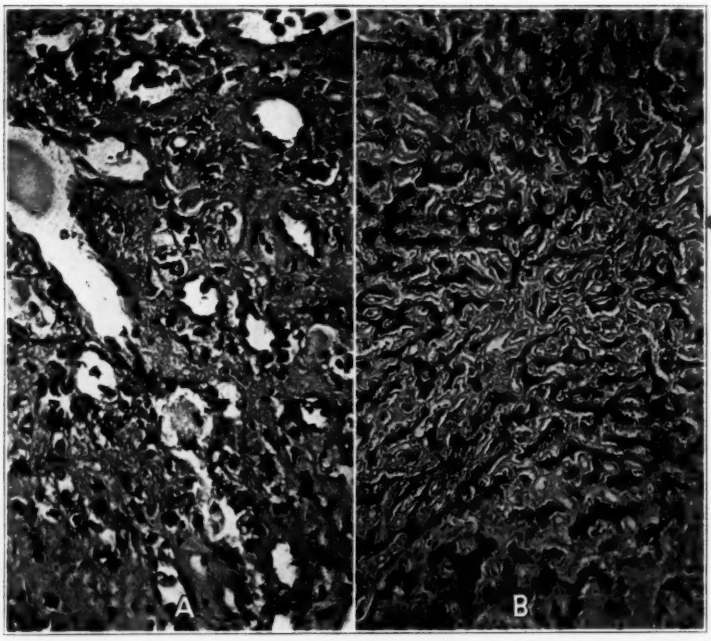

Fig. 1 (case 2).—*A*, diffuse hyaline deposits in the spleen; *B*, diffuse hyaline deposits in the liver, with atrophy of hepatic cells.

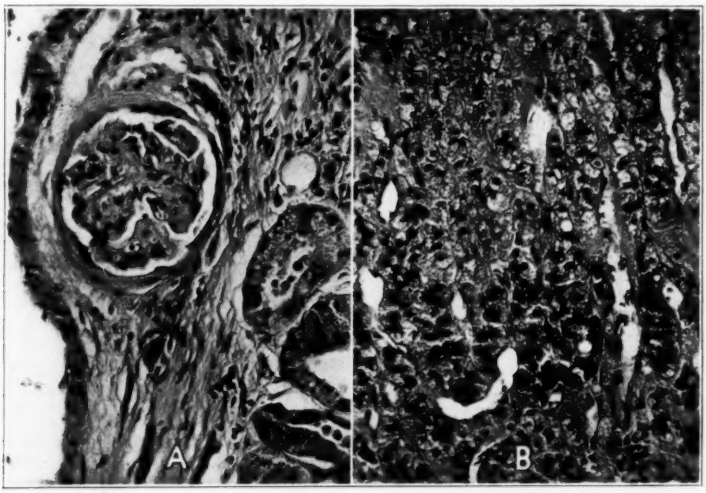

Fig. 2 (case 2).—*A*, deposits of hyaline substance in a glomerulus. Granular degeneration of tubular epithelium; *B*, hyaline deposits in a suprarenal gland. Atrophy of cortical cells.

addition, focal parenchymal atrophy with collections of lymphocytes. Epithelial cells, particularly of the convoluted tubules and Henle's loops, were swollen and contained multiple, small, eosinophilic granules. With congo red stain the hyaline substance was clearly revealed in the glomeruli, in intertubular zones and in the connective tissue of the cortical scars, as a homogeneous hyaline substance which stained bright red. Methyl violet revealed the hyaline material as light red. It was less apparent by this stain than by congo red. Large amounts of hyaline material, in bands, appeared in the suprarenal cortex, between the rows of cortical cells. Considerable atrophy of cortical parenchyma was present (fig. 2*B*). The medulla presented accumulations of hyaline deposits surrounding the vascular channels. The deposits stained characteristically with congo red. The structure of the mesenteric and pancreatic lymph nodes was replaced by an almost uniform deposit of hyaline substance beneath the sinusoidal basement membrane, accompanying general atrophy of the lymphoid cells. Staining with congo red revealed this change best. The interacinar tissue of the thyroid gland was increased in prominence, with corresponding atrophy of glandular substance, owing to homogeneous eosin-staining deposits, which gave a positive amyloid reaction with congo red.

The anatomic diagnosis was as follows: (1) generalized amyloidosis, involving the spleen, liver, suprarenal glands, myocardium, lymph nodes, kidneys, pancreas, thyroid gland, lungs, thymus, stomach and other organs; (2) hypertrophy of the liver (3,187 Gm.; normal, 1,800 Gm.) with atrophy of hepatic cells, icterus and ascites (amyloid); (3) hypertrophy of the spleen (500 Gm.; normal, 150 Gm., amyloid); (4) bilateral hydrothorax and edema of the lungs; (5) focal atrophy of the kidneys (amyloid, chronic pyelonephritis); (6) acute tubular degeneration of the kidneys; (7) cholelithiasis (one stone); (8) healed tuberculosis of the hilar nodes of the lungs, and (9) arteriosclerosis, graded 2.

CASE 3.—*History.*—A man, aged 55, was admitted to the clinic on April 5, 1932. He stated that he had felt very well until some time in the late summer of 1931, when he had begun to have epigastric discomfort which consisted of accumulation of gas, distress and a sensation of fulness occurring immediately after meals. Shortly after the onset of illness he had begun to notice shortness of breath on exertion, occasional dizzy spells and the need of urinating two or three times nightly, without other urinary symptoms. In January, 1931, he had noticed edema of the lower extremities, and at about the same time troublesome diarrhea had developed and persisted. He had consulted a physician as to treatment for the diarrhea and the edema, but a diagnosis had not been made. At this time he had begun to experience real epigastric pain for the first time, which occurred from two to three hours after meals, and occasionally awakened him at night. In February, edema of the left hand, arm and genitalia had developed. In March, the gastric discomfort after meals again had become more troublesome, and at that time he had begun to notice marked anorexia, nausea and, on a few occasions, vomiting. He had become progressively weaker and had lost flesh, and the edema had gradually increased.

Examination.—On examination the patient appeared to be anemic and somewhat cachectic. There was marked edema of the lower extremities, genitalia and left arm and hand. A moderate amount of ascites, with considerable edema of the abdominal wall and back, was observed. The blood pressure was 90 systolic and 60 diastolic, in millimeters of mercury. Daily urinalysis revealed albuminuria, graded 2 to 3. The test for bile was always positive. Hyaline casts were present, graded 2 to 3 in all specimens. There were occasional erythrocytes in a few specimens. The specific gravity was normal, ranging from 1.012 to 1.026 and averaging

around 1.020. Excretion of phenolsulphonphthalein was 50 per cent in one hour and fifteen minutes. The concentration of hemoglobin was 68 per cent (Dare); erythrocytes numbered 3,700,000 and leukocytes, 4,800 in each cubic millimeter of blood. The value for urea on two occasions was 18 and 20 mg. in each hundred cubic centimeters of blood. The concentration of cholesterol was 130 mg. in each hundred cubic centimeters of blood, and the value for proteins, 3 Gm. in each hundred cubic centimeters of serum. The value for bilirubin was 1.7 mg. in each hundred cubic centimeters of serum, and the van den Bergh reaction was direct. The stool was normal. The ocular fundi were normal, except for slight attenuation of the retinal arteries. Because of the patient's weakened condition, roentgenograms of

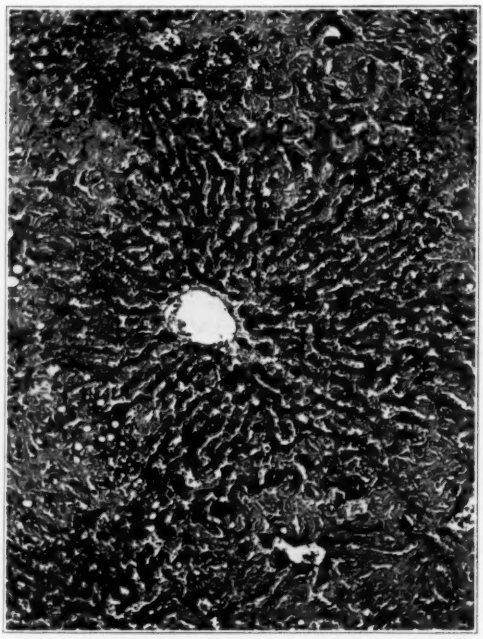

Fig. 3 (case 3).—Deposits of amyloid about the periphery of the hepatic lobule.

the stomach were not made, even though the history indicated disease of the stomach. The basal metabolic rate was —8 per cent.

Course.—During the two weeks that this patient was in the hospital under our observation, the temperature and pulse rate remained normal. The condition did not improve, however, and soon he began to fail. He refused to take adequate nourishment and did not respond to any form of symptomatic or diuretic treatment. All laboratory data pointed to chronic nephrosis, but this did not satisfactorily explain his appearance and certain other features. He looked too sick and cachectic for this diagnosis, and a malignant condition was suspected. The low value for blood cholesterol was also against the diagnosis of chronic nephrosis with edema.

Death occurred before a contemplated congo red test for amyloid disease could be carried out. Necropsy was performed nine hours after death.

Necropsy.—Moderate edema of the lower extremities was present. The left pleural cavity contained 1,000 cc. of clear, straw-colored fluid. The heart weighed 198 Gm. The spleen weighed 261 Gm., and was slate blue and of firm consistence. The cut surface was mottled by dark grayish, pinpoint markings, the remainder of the spleen appearing light red. Iodine gave the darker markings a reddish-brown hue. The liver was normal in appearance. Iodine, applied to the sectioned surface, failed to give an amyloid reaction. Beginning on the anterior wall of the greater curvature, 7 cm. below the cardia, the stomach was involved in an extensive neoplastic process. The area involved almost the entire fundus. A few small, sessile, polypoid masses projected from the surface of the growth. The serosa along the greater curvature and the lymph nodes along the lesser curvature

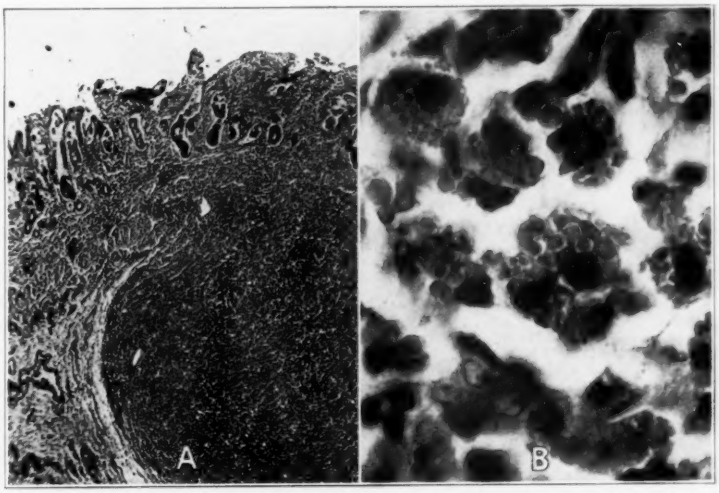

Fig. 4 (case 3).—*A*, low power view of the gastric carcinoma, revealing the medullary and infiltrative characteristics; *B*, high power view of the gastric carcinoma. The acidophilic cells, containing eosinophilic granules, are well shown.

were involved. The cortex of the left suprarenal gland was atrophic. The right kidney weighed 160 Gm. and the left, 201 Gm. An amyloid reaction was not elicited by iodine. The myocardium, stained with congo red for microscopic examination revealed, in many arterioles, a varying amount of hyaline, red-staining material. Occasionally, small amounts of a substance of similar appearance were observed in the stroma, and about these zones muscular atrophy was apparent. Sections of the spleen disclosed focal deposits of an eosin-staining, hyaline substance, situated in the zones of the malpighian corpuscles. In the sections stained with congo red, this hyaline material stained brilliantly red. By staining with methyl violet, the hyaline material appeared light red or pink. Iodine gave the hyaline deposits a reddish-brown hue. This color was not changed by the addition of sulphuric acid. The liver revealed hyaline, eosin-staining, hemogeneous deposits usually about the periportal spaces or circumscribing the peripheral third of the

hepatic lobule (fig. 3). With congo red, the hyaline replacements were observed to stain intensely red. Methyl violet gave only a slight suggestion of the metachromatic reaction characteristic of amyloid. Iodine, however, imparted to the substance a reddish-brown hue, which was neither intensified nor changed by the addition of sulphuric acid. Sections of the gastric neoplasm disclosed an infiltrating, medullary type of carcinoma simplex, composed of large, rounded or polygonal cells, the cytoplasm of which was extensive and usually distinctly acidophilic. A small amount of stroma and a few vascular channels completed the picture (fig. 4*A*). Under higher magnifications, the cytoplasm of the acidophilic cells was seen to contain rather large, hyalin-like, eosinophilic granules (fig. 4*B*).

Fig. 5 (case 3).—Two glomeruli revealing deposits of amyloid.

Mitotic figures were fairly numerous, or, as seen in other cells, the nuclei were large and hyperchromatic or undergoing retrogressive changes, such as pyknosis and karyorrhexis. At the periphery of the growth the gastric mucosa was undermined by the malignant cells. The muscular coats of the stomach and the serosa were involved. The eosinophilic, cytoplasmic granules of the "acidophilic neoplastic cells" did not react with either iodine or methyl violet stain. Throughout both suprarenal glands there was atrophy of the cortical parenchyma at the expense of intercellular hyaline deposits, which stained with congo red, as amyloid. The kidneys disclosed only focal, hyaline thickening of glomerular tufts. Congo red revealed this change as amyloid (fig. 5). A few similar deposits were seen in the walls of the intertubular, renal blood vessels and stroma.

The anatomic diagnosis was as follows: (1) carcinoma of the stomach, probably of the acid-cell type; (2) generalized amyloidosis, involving the liver, spleen, kidneys and suprarenal glands; (3) hypoplasia of the heart (198 Gm.; normal, 250 Gm.) with calcareous deposits in the mitral valve, and (4) hydrothorax on the left side (1,000 cc.) and slight edema of the lower extremities.

COMMENT

Clinical Features.—In case 1, a diagnosis of acute nephritis was practically excluded by the history and by the fact that the patient's condition was too grave to be explained by acute nephritis in the absence of a higher degree of renal insufficiency. Furthermore, the absence of edema and anemia, the presence of hypotension and the fact that the urine had a specific gravity of only 1.015, although loaded with albumin, were against such a diagnosis. Subacute or chronic glomerulonephritis was unlikely because of the low blood pressure and the absence of anemia, and because the patient was too sick for the degree of renal insufficiency that could be demonstrated. Chronic lipoid nephrosis was easily ruled out by the absence of edema and the presence of hematuria. Pyelonephritis and acute toxic nephrosis were readily dismissed after momentary consideration.

We realized, then, that the data in this case were atypical for any of the ordinary forms of nephritis mentioned, and it was naturally deemed advisable to exclude other possibilities, such as Bence-Jones proteinuria with renal insufficiency[3] or amyloid disease, even though there was no reason to suspect the presence of either.

Bence-Jones protein was not present, but the congo red test for amyloid disease was strikingly positive, and after tests of hepatic function had indicated extensive involvement of the liver, the diagnosis of diffuse amyloidosis was correctly made.

Likewise, in case 3, the marked edema, the heavy albuminuria, the hypotension, the very low value for serum protein, with inversion of the albumin-globulin ratio, all suggested chronic nephrosis with edema. The low value for blood cholesterol, however, practically excluded lipoid nephrosis, especially since there were other atypical features, such as slight anemia and an abnormal number of erythrocytes in the urine. Furthermore, the patient appeared too ill to allow a diagnosis of ordinary chronic nephrosis. This raised the possibility of a nephrotic stage of chronic glomerulonephritis, but he was too sick to allow of this diagnosis also, considering the normal values for blood urea and the normal rate of excretion of phenolsulphonphthalein; moreover, he had

3. Bannick, E. G., and Greene, C. H.: Renal Insufficiency Associated with Bence-Jones Proteinuria: Report of Thirteen Cases with a Note on the Changes in the Serum Proteins, Arch. Int. Med. **44**:486 (Oct.) 1929.

hypotension rather than hypertension. A cardiac basis for his disability was easily excluded. The extremely low value for serum proteins aided in ruling out cardiac dropsy, for in this condition it would be normal or increased; the patient, furthermore, did not have a diuretic response to salyrgan that would have characterized cardiac dropsy. The direct van den Bergh reaction of the serum bilirubin suggested a hepatic basis for the ascites and edema, but, again, the low value for serum proteins, the marked albuminuria and the early occurrence of edema of the left arm, abdominal wall and other regions proved that other important factors were present.

The patient appeared cachectic, and the probability of malignancy was immediately considered, but this did not explain all the data. Therefore, final analysis of the history and data in this case suggested a diagnosis of a malignant condition, probably of the stomach because of the history, but this diagnosis was inadequate; it suggested a diagnosis of hepatic disease, but this also was inadequate and it suggested the diagnosis of nephrosis, which in its turn was inadequate.

The best explanation of the combination of conditions was that the patient had a malignant disease, with diffuse amyloidosis and amyloid nephrosis; this diagnosis was tentatively made, and a congo red test was requested for confirmation. We feel certain that this would have shown the characteristic response and resulted in a definite and accurate diagnosis.

In case 2 the diagnosis of diffuse amyloidosis was not made by any of the physicians who saw the patient in this clinic or in two large clinics elsewhere; yet all appreciated that they were dealing with an unusual case of hepatic disease of some sort, and those in attendance during the patient's terminal illness at this clinic observed that a combination of profound renal, suprarenal and hepatic insufficiency was manifested. By employing the same line of reasoning and exclusion as that outlined in cases 1 and 3, and as emphasized previously, diffuse amyloidosis might have been suspected, and a congo red test probably would have resulted in a correct diagnosis even though the etiology remained obscure.

We have felt justified in predicting that congo red would have disappeared rapidly from the blood stream in cases 2 and 3 because of the very extensive deposits of amyloid, and because of the striking reaction of these deposits to congo red after death. This conclusion, we are sure, would have the approval of Bennhold,[4] who noted in his

4. Bennhold, Hermann: Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **142**:32 (March) 1923.

early work on this subject that patients with extensive amyloidosis, especially amyloidosis of the liver, practically all gave positive congo red tests, and that it was when the deposits of amyloid were not extensive that one might obtain a negative congo red test. An abstract of our experience with this test, as applied to the diagnosis of amyloid disease, has been published previously.

Pathologic Features.—The unusual features in case 2 were the development, without apparent cause, of diffuse, hyaline, amyloid-like deposits and also the character of the hyaline substance, which did not possess the usual specific staining qualities of amyloid. There were no evidences of suppuration or chronic disease, which are generally considered to be the prerequisites in the etiology of amyloidosis. The slight nodal enlargement, which suggested Hodgkin's disease clinically, did not resemble this entity pathologically. The staining reactions of the hyaline substance were never entirely characteristic for amyloid. In the fresh state the gross iodine reaction revealed a change in color to dark brown or black, never the typical reddish brown. In sections, the iodine reaction failed completely. The addition of sulphuric acid also failed to produce a response to the iodine reaction. Staining with methyl violet was partially successful, but failed to disclose the usual degree of metachromatic reaction given by amyloid. Staining with congo red demonstrated the deposits best, but this reaction is probably less specific than the other two. Other hyaline substances have marked affinity for the dye.

We may, therefore, conclude that in this case we were not dealing with true or chemically perfect amyloid, but rather with a hyaline, amyloid-like substance, possessing some and lacking other features of true amyloid, and yet best classified as amyloid.

The postmortem studies in case 3 revealed two interesting and unusual conditions: first, the peculiarities of the carcinoma of the stomach, and second, the generalized amyloidosis which was unassociated with suppuration or chronic disease other than gastric malignancy. The carcinoma had evidently been present for a long time. This fact may have significance in the pathogenesis of amyloidosis in this case. In its microscopic appearance, the malignant process was revealed as a medullary type of carcinoma simplex, with peculiar acidophilic staining of the cytoplasm of its cells. The amyloid in this case, unlike that in case 2, gave all of the typical staining reactions characteristic of amyloid. We may conclude from the staining reactions that the amyloid in case 3 was essentially of the same structure as deposits of amyloid usually are, and that its formation was in some way related to the gastric carcinoma.

SUMMARY AND CONCLUSIONS

1. Two cases of diffuse amyloidosis of unusual etiology and one case of unknown etiology are reported. In case 1, the basis for the amyloidosis was probably Hodgkin's disease, and in case 3, an unusual type of gastric carcinoma.

2. The case in which the etiology was obscure, case 2, was also atypical pathologically, in that the amyloid-like deposits did not have all of the staining characteristics of ordinary amyloid.

3. The carcinoma in case 3 was a rare form of gastric carcinoma and suggested an acid cell type.

4. Diffuse amyloidosis usually can be diagnosed if suspected. The congo red test is a valuable laboratory aid in the diagnosis of this condition.

5. Amyloidosis should be considered in the differential diagnosis of all unusual cases of hepatic, splenic, renal or suprarenal disease, even though no apparent basis for amyloidosis is noted.

6. In each of the three cases reported, suprarenal insufficiency was noted clinically, and necropsy revealed extensive suprarenal amyloidosis. In each case hypotension was striking, and in cases 1 and 2 the crisis of Addison's disease was simulated, but in no case was there abnormal pigmentation.

Book Reviews

Endocrine Medicine. By William Engelbach. Volume I. General Considerations. Volume II. The Infantile Endocrinopathies. Volume III. The Adolescent Endocrinopathies: The Adult Endocrinopathies. [Volume IV, containing Bibliography and Index, will be issued later.] Cloth. Price, $35 per set. Pp. 460, with 138 illustrations; 473, with 214 illustrations; 862, with 366 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

"When a man's knowledge is not in order, the more of it he has the greater will be his confusion." This is the embarrassing situation, certainly, in which most physicians have found themselves as regards the relation of the endocrine glands to medicine. As a matter of fact, one wonders whether endocrinology as a workable "specialty" is destined to endure either in physiology or in clinical medicine. Diabetes has long since and by common consent detached itself, because, as every one knows, special training in physiologic chemistry and in nutrition is necessary for the adequate handling of diabetic problems. The endocrinology of the female is being preempted more and more by men with a sound gynecological background; the recent dramatic progress in the knowledge of disorders of the parathyroid gland comes from physiologically minded and chemically trained internists, and physiologists and general internists seem to be on the front line of the recent advances in the suprarenal problem. So that stripped of its trappings little more remains than a straw man destined to be picked to pieces by the expert in heredity, in anthropometry and in chemistry, as well as by the surgeon, gynecologist and internist.

It is with great interest, therefore, that one approaches this latest work on endocrine medicine, and surely there is here a vast and valuable compendium of knowledge. History, anatomy, physiology and chemistry, as well as more immediately practical matters, such as the methods of examination, clinical findings and treatment, are all dealt with at length. The first volume on general considerations—"happy prologues to the swelling act"—is the most satisfactory; the later sections lose force because of the division into infantile, juvenile, adolescent and adult endocrinopathies, an arrangement which makes for repetition and offers difficulties in the pursuit of any single thread through the whole tangle. One could also wish that the author had taken a more definite stand about certain matters; the reader is too often left to choose for himself from a variety of theories or modes of procedure, some of obviously doubtful soundness; in the section on hyperthyroidism, for example, one does not discover how the author really feels about the question of so-called toxic adenoma versus exophthalmic goiter. With some of the "pituitary syndromes" and "gonadal syndromes," on the other hand, the reader, or at least the reviewer, is left confused as well as unconvinced that there is a sound basis for the claims of clinical classification. To be frank, the reviewer is disappointed in the clinical sections. No vivid pictures of disease appear: there is a disjointed assembly of ill-balanced material rather than a smooth and convincing story. Furthermore, the discussions, though lengthy, are often incomplete and inadequate. On various occasions, for example, one is told that the differential diagnosis of a condition is made by ruling out other possibilities, but what these possibilities are or how they are to be excluded is not revealed. But leaving aside such minor criticisms and turning to the positive merits of the work, there is an excellent collection of well illustrated and well documented case reports, even though the patient is often "put through the mill" and many of the tests have no bearing on the problem. The format is attractive and does credit to Mr. Thomas' interest in producing fine books.

In these days when accurate and elegant use of words in medical writing seems to be considered of no special importance, one hardly knows whether to

comment on literary style, but certainly the three graces of rhetoric—clearness, force and precision—did not assist at the birth of this compilation. The coining of new and impossible words to which the author frequently resorts, as well as the misuse of a word which resembles the one he evidently intended to use, is somewhat annoying; for example, rapid scientific "advancements" for rapid scientific "advances"; the "solicitation" of an anamnesis for the "eliciting" of an anamnesis, and the "purport" of this chapter for the "purpose" of this chapter. The statements that "relative unimportance will be placed" and that certain diseases are common in "juvenility," as well as the reference to Roger of Palermo as "the Salernitan surgeon," are disturbing to the language-conscious reader, and such a statement as "the measurements have been limited to seven, and, for the practical purposes of this Country, given in inches and the weight in pounds" (vol. 1, p. 265) is grammar so bad as to be beyond remedy. By "progesteral" effects, one supposes that the writer means "progestational" effects (vol. 1, p. 15.).

The Failing Heart of Middle Life: The Myocardosis Syndrome, Coronary Thrombosis, and Angina Pectoris, with a Section upon the Medico-Legal Aspects of Sudden Death from Heart Disease. By Albert S. Hyman, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals; Attending Physician and Cardiologist, Hospital for the Aged; Consulting Cardiologist, Harlem Day Nursery; Chief, Cardiac Clinics, Beth David and Manhattan General Dispensaries; Director, Witkin Foundation for the Study and Prevention of Heart Disease, New York, and Aaron E. Parsonnet, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital; Cardiologist, Evening Heart Clinic, Newark Beth Israel Hospital; Medical Director, Home for the Aged; Fellow, Witkin Foundation for the Study and Prevention of Heart Disease, Newark, N. J. With a preface by David Riesman, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia. Cloth. Price, $5. Pp. 538, with 166 illustrations. Philadelphia: F. A. Davis Company, 1932.

The increasing incidence of degenerative heart disease and its encroachment on the younger age groups have impressed every one who comes in contact with diseases of the heart. The present work deals with this type of disorder. Although the work is entitled "The Failing Heart of Middle Life," the authors have determined the period of middle life, not by the calendar, but by the condition of the coronary arteries. The book is somewhat unique in that it deals largely with the type of disorder that is not the result of disease but of degenerative processes. The patients described were free from trouble until a diminished cardiac function appeared. To this condition they have applied the term the myocardosis syndrome, by which they distinguish it from heart disease of inflammatory origin. They stress further the importance of searching for certain signs and symptoms by which the degenerative process may be discovered before heart failure becomes a prominent symptom.

The book is divided into six sections. The first deals with the normal and pathologic coronary arterial system. This section is well supplied with photographs, photomicrographs and diagrams illustrating the coronary circulation in health and disease. The original work of Dr. Yaguda adds much to the value of this section.

The second part defines and describes the mycardosis syndrome.

The third part deals with thrombosis of the coronary arteries. The symptoms, findings, complications, prognosis and treatment are adequately considered.

Electrocardiographic changes due to coronary disease are considered in the fourth part. In such a debatable field as this, one which is undergoing daily revisions and modifications, statements will be found that will not meet with universal endorsement. The discussion, however, is excellent, and no major criticism may be offered.

Angina pectoris, another debatable and complex subject, is discussed in part five.

Part six is another unique feature, a medicolegal discussion of sudden death from heart disease. This section is interesting and very likely valuable, but it is beyond the reviewer to comment on its accuracy.

A bibliography of about 1,250 references completes the work.

The book is well written and readable It will have a special appeal to the student and the general practitioner, to whom it is highly recommended.

Organs of Internal Secretion. By Ivo Geikie Cobb. Fourth edition. Price, $3.50. Pp. 303. Baltimore: William Wood & Company, 1933.

This book first appeared in 1916. It is presumably a presentation of the latest known facts concerning the glands of internal secretion, but as has happened so often in books of this kind, there is no sharp distinction drawn between facts and fancy, nor is the book in any way a critical exposition of endocrinology. A few excerpts picked at random will illustrate this. On page 144 the statement is made that "the present writer has been utilizing padutin in a limited number of cases of arterial hypertension and it appears to produce a lower blood pressure with increased comfort to the patient." On page 160 it is stated "that the mammary gland extract is capable of stopping excessive menstrual flow and will also remedy too frequent menstruation." On page 165, quoting from another author, "a course of treatment of testicular extract frequently accomplishes such a number of changes of such remote organs, and influences such widely disconnected ones, that to report actual results might even be sufficient to discount the position of this method. . . . There are a few single remedies which can compare with active and properly prepared testicular extracts." On page 169 it is stated that "many pluriglandular preparations contain an extract of one of the gonads as a component part. . . . Many manufacturers are now placing on the market standardized solutions for hypodermic or intramuscular use. Where it is feasible, it is a more direct, and probably a more efficacious, method to administer these substances by the hypodermic route." On page 235 one finds, "for the neurasthenic patient, the extracts of the gonads, either alone or combined with extracts of nervous tissue, are frequently of great help." Pluriglandular preparations are recommended here and there throughout the book for the treatment of many conditions. "A general endocrine tonic will contain extracts of nervous tissue with perhaps a small dose of thyroid and pituitary and some orchitic or ovarian tissue." These quotations exemplify the absence of a critical attitude in presenting the subject matter. In the expressions of endocrine disorder the book may be considered reasonably sensible, but in the question of therapy, the realms of fancy are certainly reached. The most recent work of Collip, Hartmann, Doisy, Rogoff and others is merely mentioned. Very little attention is paid to the latest important studies of the female sex hormone; about a third as much is paid to the male gonads. Many of the statements made by the author are compiled from the literature of manufacturing houses and endocrinologic quacks, indicating the type of book that is being reviewed. It cannot be recommended.

Clinical Diagnosis: Physical and Differential. By Neuton S. Stern, M.D., Associate Professor of Medicine, University of Tennessee School of Medicine. Price, $3.50. Pp. 364. New York: The Macmillan Company, 1933.

Many a clinician, in the depths of his heart, feels that some day he will write the most perfect volume on clinical diagnosis ever put forth. Therefore, because of this feeling, he may appear to be unduly critical of new books on this subject as they appear from time to time.

Dr. Stern's "Clinical Diagnosis" is a nice appearing volume of convenient size, and it is well printed. It is written logically and clearly and contains a great deal of sound information. Anatomically, it is divided into four parts. The first deals with the taking of a history and physical examination, seven pages being devoted to the former topic and more than a hundred to the latter.

The second part deals with symptoms and signs in pulmonary tuberculosis and cardiac disease, only ten pages being devoted to the subject of tuberculosis and more than fifty to the heart.

The third part deals with the principles and practice of differential diagnosis, and includes a series of twenty-one "paper cases." These can be utilized in classwork according to the method found successful by Dr. Richard C. Cabot about twenty-five years ago.

The fourth part is a short glossary and defines with more or less detail about one hundred medical expressions and terms. Of this part, the most ingenious bit is a description of the interpretation of electrocardiograms, with a schematic representation of what a normal tracing looks like and of the abnormalities most commonly encountered.

Critical-minded folk, perhaps, will hope to see the second edition of this book lay more emphasis on the taking of a history and less on cardiovascular examination, more on the fact that careful pelvic and neurologic examinations should be considered as a part of a general physical examination and less a special one. But these, after all, are minor weaknesses. Without doubt, the book is a good one, and will prove helpful to students.

Biochemistry in Internal Medicine. By Max Trumper, Ph.D., and Abraham Cantarow, M.D. Price, $5.50. Pp. 454. Philadelphia: W. B. Saunders Company, 1932.

This book is intended to supply the physician or the medical student with an interpretation of the biochemical methods used in routine and more exacting laboratory studies. It is a good bridge over the gap between the clinical and the more abstract biochemical studies. The authors rarely refer to the actual laboratory procedures, but emphasize the interpretations and applications of the results found by the modern methods. The metabolism of carbohydrates, proteins, cholesterol, chloride, calcium and phosphorus is presented in a concise and clear manner with possibly too little criticism of the true absolute values of the quantities reported by different methods in some estimations. Cholesterol is referred to as "a mixture of two or more sterols." Acid-base balance is presented in a clear and readable style with emphasis on the more important mechanisms involved in the control of the p_H of the blood. The method followed in attempting to explain the p_H may be questioned. Naturally much of the material mentioned is again presented in an organized scheme under the discussion of basal metabolism, diabetes mellitus, renal function, nephrosis, hepatic function, gastric function, pancreatic function, changes in pregnancy and lactation and composition of cerebrospinal fluid transudates, exudates and edema fluid. The usual miscellaneous chemical findings on urine are dealt with, and finally the reader is supplied with normal values on various body fluids and an outline enumerating chemical changes associated with various clinical diagnoses.

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